Phase 1/2a Study of RX-5902 in Advanced Solid Tumors (ST): an Orally Bioavailable Inhibitor of Phosphorylated p68 and Modulator of β-Catenin Nuclear Translocation

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Background
RX-5902 is a novel compound targeting phosphorylated p68 (p-p68) RNA helicase (ie, DDX5), a member of the DEAD box family of RNA helicases. P-p68 may play a role in cell proliferation and cancer progression by locking the nuclear translocation of β-catenin. Final data from the first clinical study of single agent RX-5902 to treat solid tumors and the ongoing Phase 2a in advanced triple-negative breast cancer (TNBC) and ovarian cancer (OC) are described.

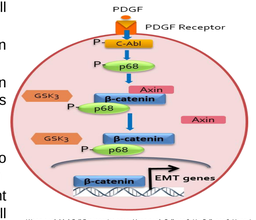
Methods
This is a Phase 1/2a study (NCT02003092) designed to evaluate safety, tolerability and pharmacokinetics (PK) following increasing doses of RX-5902 at varying schedules. Primary objectives include safety, tolerability and dose limiting toxicities to identify the maximum tolerated dose and a recommended phase 2 dose and schedule (RP2D). Secondary objectives were PK and antitumor activity. Eligible subjects (aged ≥ 18 years) with relapsed/refractory ST 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.

Results
As of May 2016, 24 subjects were enrolled (11 Females, 13 males). No dose limiting toxicities or treatment related SAEs were reported. Seven subjects experienced stable disease (breast, neuroendocrine, paraganglioma, head/neck and colorectal cancers); 3 subjects received treatment for > 1 year. The most common side effects were grade 1 related adverse events: nausea, vomiting and fatigue; no grade 2 related events were reported. RX-5902 was orally bioavailable with median Tmax of 2 hours and half-life of 12 hours. Doses were successfully escalated to 300 mgs daily for 5 days, with a 3 weeks on, 1 week off schedule. Daily doses of 300- 400 mgs daily for 28 days are being tested.

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, squamous cell cervical and colorectal cancers. Final results from the phase 1 and data on the first stage of the Phase 2a in patients with TNBC and advanced OC 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 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.

Subject Demographics and Prior Treatments

Parameter	Overall
Gender, n (%)	31
Female	17 (55%)
Male	14 (45%)
Median age (range)	58 (25-86)
Race, n (%)	
White	31 (100%)
ECOG performance status, n (%)	
0	9 (29%)
1	22 (71%)
Number of prior anticancer treatments, n (%)	
1	3 (10%)
2	4 (13%)
3	7 (22%)
4+	17 (55%)

Safety Profile

Adverse Event	Related Events		Highest Severity Grade Per Related AE (N)			
	N	%	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	10	37	3	5	2	0
Nausea	8	30	5	3	0	0
Vomiting	4	15	4	0	0	0
Anorexia	4	15	3	1	0	0
Diarrhea	4	15	2	2	0	0
Insomnia	3	11	2	1	0	0
Constipation	2	7	2	0	0	0
Cognitive disturbance	2	7	0	1	1	0
Hyponatremia	2	7	0	0	1	1
Weight loss	2	7	2	0	0	0
Generalized weakness	2	7	1	0	1	0
Myalgia	2	7	2	0	0	0
Somnolence	2	7	0	2	0	0

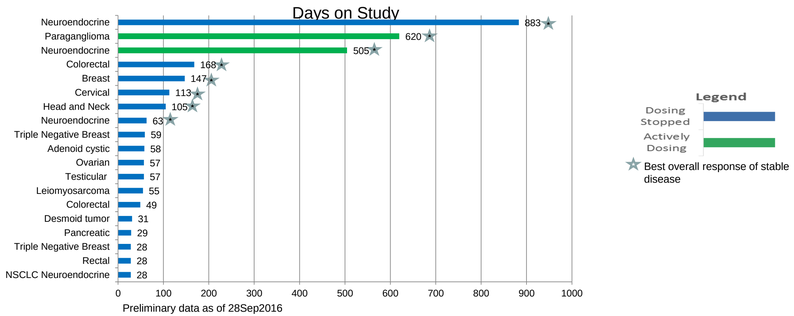
Pharmacokinetics

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. PK parameters of multiple weekly dosing schemas are shown below.

Dose (mg)	N	Dose Scheme	Dose Number	Cmax (μg/L)	Tmax (hr)	T1/2 (hr)	AUClast (hr*μg/L)
250	1	3 / Week	1	394	2	14	5211
250	1	3 / Week	7	403	2		7774
300	1	3 / Week	1	288	6	10	4555
300	1	3 / Week	7	301	2		4143
150	1	5 / Week	1	227	2		2152
150	1	5 / Week	11	347	1		3721
200	1	5 / Week	1	337	4	9	2752
200	1	5 / Week	11	440	2		4034
300	4	5 / Week	1	477	2	11	3821
300	3	5 / Week	11	395	2		3262
300	5	7 / Week	1	501	3		2534
300	1	7 / Week	15	1250	6		4477

Pharmacokinetic profiles of RX-5902. Dose proportional increase in plasma exposure, with slight accumulation from Days 1 to 15. Rapid oral absorption, with elimination half life suitable for once daily dosing. Predictive population PK model built based on subject data.

Best Overall Response in Evaluable Subjects



Preliminary data as of 28Sep2016

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.
- The maximum tolerated dose or recommended phase 2 dose has not been determined yet.
- 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