Results of a Phase 1 Study of Single Agent RX-3117: An Oral Antimetabolite Nucleoside to Treat Solid Tumors

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Abstract # 2555

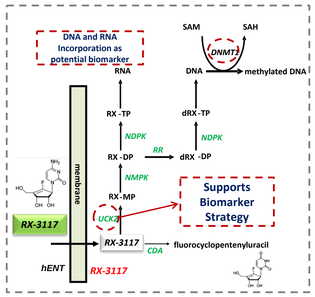
Background: RX-3117 is an oral small molecule antimetabolite, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117 has shown efficacy in xenograft models of gemcitabine resistant pancreatic, bladder and colorectal cancer. Emerging data from a Phase 1 clinical study of RX-3117 as a single agent in subjects with solid tumors is described below.

Methods: The Phase 1 study (NCT02030067) is designed to evaluate safety, tolerability and pharmacokinetics (PK) following increasing doses and schedules of RX-3117 in eligible subjects (aged ≥ 18 years) with relapsed/refractory solid tumors. Primary objectives include safety and tolerability to determine the MTD and a recommended phase 2 dose and schedule (RP2D); secondary objectives were PK and antitumor activity (RECIST v1.1). Subjects received oral RX-3117 3, 5 or 7 times per week for 3 weeks followed by 1 week of rest or 4 weeks without a rest for up to 8 cycles. Plasma concentrations were measured using a validated LC-MS/MS assay, and noncompartmental pharmacokinetic parameters were calculated using WinNonlin, Version 6.4.

Results: As of Jan 2016, 41 subjects have been enrolled (26 Females, 15 males). Eleven subjects experienced stable disease for 1 to 10 cycles; with 7 subjects receiving treatment from 104 to 276 days. A tumor burden reduction was seen in 3 subjects with pancreatic, breast and mesothelioma cancers. RX-3117 PK demonstrated a dose proportional exposure and was rapidly absorbed without a marked lag time, and with a median Tmax between 2 to 3 hours; accumulation was generally minimal. The most frequent related adverse events were moderate to severe anemia, mild to moderate fatigue and nausea, mild diarrhea, vomiting, and anorexia. Dose limiting toxicity of anemia was observed at 2000 mg administered 3 times per week. The recommended phase 2 dose and schedule will be 700 mg 5 times per week.

Data from this study RX-3117 is safe and well tolerated at the doses and schedules tested. Early antitumor activity has been observed in pancreas, colorectal and mesothelioma cancers. A 2 stage Phase 2A design for pancreatic and bladder cancers is ongoing.

RX-3117 Proposed Mechanism



	Gemcitabine	RX-3117
1. Phosphorylation (activation) Enzyme	Deoxycytidine kinase (dCK)	Uridine-cytidine kinase 2 (UCK2)
2. Degradation by Cytidine Deaminase	Fast deamination	Slow deamination
3. DNA Methyl – transferase 1 Activity	Yes	Yes
4. Membrane Transport	hENT - dependent	hENT - dependent
5. Incorporation	DNA & RNA	DNA & RNA
6. Synthesis Inhibition	DNA & RNA	DNA & RNA

Study Design

This is a Phase 1 multicenter, dose finding, open-label, dose expansion, single agent study of RX-3117 administered orally to subjects with advanced or metastatic solid tumors. One subject was treated per dose group until the appearance of a related grade 2 or greater adverse event, after which 3 subjects were treated using a modified Fibonacci schedule. The study has been amended to allow a 2 stage phase 2 study design that treats subjects with metastatic pancreatic or bladder cancer. Preliminary data from stage 1 is also presented.

For further information about RX-3117 and Rexahn Pharmaceuticals
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Patient Demographics and Prior Treatments

Parameter	Overall
Gender, n (%)	45
Female	30 (66.7%)
Male	15 (33.3%)
Median age (range)	61.7 (45-87)
Race, n (%)	
White	35 (66.7%)
Black	2 (4.4%)
Asian	1 (2.2%)
Other	5 (11.1%)
ECOG performance status, n (%)	
0	6 (13.3%)
1	35 (77.8%)
2	4 (8.9%)
Number of prior anticancer treatments, n (%)	
1	6 (13.3%)
2	6 (13.3%)
3	14 (31.1%)
4+	20 (44.4%)

Baseline Characteristics of Patients. 48 potential patients were screened of which 45 were enrolled and treated with RX-3117.

Safety Profile

Adverse Event	Number of Subjects per severity grade, n			
	Grade 1	Grade 2	Grade 3/4	Overall
Anemia	3	7	5/0	15
Anorexia	7			7
Dehydration		2		2
Diarrhea	6	3		9
Fatigue	15	8		23
Hypokalemia		2		2
Lymphocyte count decreased			2/0	2
Nausea	12	5		17
Neutropenia		1		1
Oral Mucositis			1/0	1
Platelet Count decreased	1			1
Thrombocytopenia	1	1	1/1	4
Vomiting	7	2		9
White Cell Decreased			0/1	1

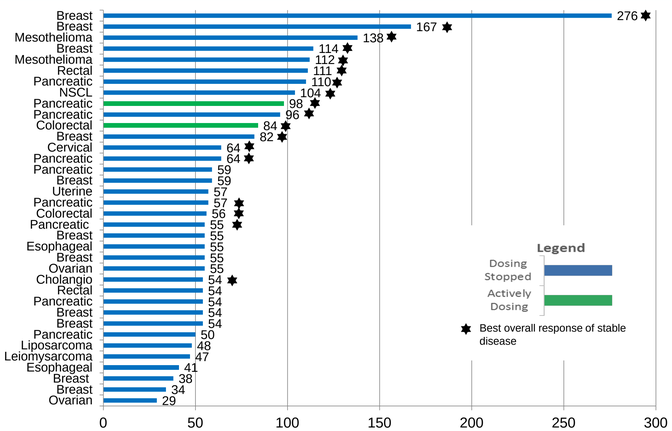
Two DLTs were observed; Grade 3 anemia at the 2000 mg dose administered weekly and Grade 3 oral mucositis at 500 mg administered 7 times per week. Both events were reversible.

Pharmacokinetics

Pharmacokinetic samples were collected on Days 1 and 15 for 48 hrs. Plasma concentrations were measured using a validated LC-MS/MS assay, and non-compartmental PK parameters were calculated using WinNonlin. Values for Day 1 shown below; similar results were obtained for Day 15 (doses < 200 mg not shown).

Dose (mg)	Frequency	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)	AUC_{0-24} (hr*ng/mL)	Comment
200	3 per Week	637	2	13.3	4719	
500	3 per Week	1104	2	16.7	7916	
1000	3 per Week	1635	2	11.6	12218	
1500	3 per Week	1622	3	11.8	15322	
2000	3 per Week	1858	3	13.3	17044	1 DLT (anemia)
500	5 per Week	1441	2	7.2	12373	
700	**5 per Week**	**989**	**3**	**9.1**	**8663**	**RP2D**
500	7 per Week	1269	3	8.3	10097	1 DLT (Oral mucositis)

Treatment (Days) and Best Response



A tumor burden reduction was seen in 3 subjects with pancreatic (marked reduction in CA19-9), breast (15% reduction in a liver lesion), and mesothelioma (9% in tumor volume) cancers

Conclusions

- RX-3117 is safe and well tolerated at the doses and schedules tested. The recommended Phase 2 Dose is 700 mg administered for 5 consecutive days with 2 days off for 3 weeks with 1 week off.
- Early anti-tumor activity was observed in patients with pancreatic, colorectal, breast, mesothelioma and non-small cell lung cancers
- Phase 2a study in advanced pancreatic cancer and muscle-invasive bladder cancer is ongoing

Investigator Disclosures

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