RX-3117, An Oral Antimetabolite to Treat Advanced Solid Tumors (ST): Phase 1 and Ongoing Phase 2a Results

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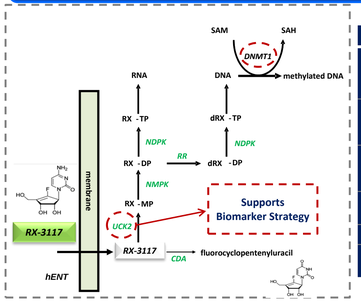
Background: RX-3117 is an oral small-molecule antimetabolite cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117 shows efficacy in various xenograft models, including those of gemcitabine resistant pancreatic, bladder and colorectal cancers. Data from a Phase 1/2a clinical study of RX-3117 as a single agent in subjects with advanced ST are described below.

Methods: The Phase 1/2a 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 ST. 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. Subjects received oral RX-3117 at 3, 5 or 7 times per week for 3 weeks with 1 week of rest in each 4 week cycle. Phase 2a is ongoing in patients with pancreatic or bladder cancer in a 2-stage design, where 10 patients will be treated and if 2 responses are seen, 40 additional patients will be added to the corresponding arm.

Results: As of May 2016, 48 subjects were enrolled (30 Females, 18 males), with 4 subjects enrolled in the Phase 2a portion. Sixteen subjects experienced stable disease for 1 to 10 cycles; with 11 subjects treated from 82 to 276 days. A tumor burden reduction was seen in 3 subjects with pancreatic, breast and mesothelioma cancers. RX-3117 PK was dose proportional and was rapidly absorbed with a median T_{max} of 2 to 3 hours; accumulation was 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 RP2D is 700 mg for 5 consecutive days per week, 3 weeks on, one week off, per 4-week cycle.

Conclusions: RX-3117 is safe and well tolerated. Early anti-tumor activity has been observed in pancreas, colorectal and mesothelioma cancers. The 2-stage Phase 2a trial for pancreatic and bladder cancers is ongoing. Final results from the phase 1 and data on the first stage of the Phase 2a will be presented.

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: DNA Hypomethylation
4. Membrane Transport	hENT - dependent	hENT - dependent
5. Incorporation	DNA & RNA	DNA & RNA
6. Synthesis Inhibition	DNA & RNA	DNA & RNA

Study Design

The initial Phase 1 was a multicenter, dose finding, open-label, dose expansion, single agent study of RX-3117 administered orally to subjects with advanced or metastatic solid tumors. An additional 12 subjects were treated with the RP2D of 700 mg 5 times per week for 3 weeks in each 4 week cycle.

Phase 1b/2a 2-Stage:

The Phase 1 study was amended to allow a 2-stage phase 1b/2a study design to treat subjects with metastatic pancreatic or bladder cancer with single agent RX-3117 at the dose and schedule identified in Phase 1. Stage 1 was planned to treat 10 subjects with metastatic pancreatic cancer. Advancement to stage 2 was predefined as 20% or more subjects with progression free survival of ≥ 4 months or a partial/complete response in at least 10% of subjects.

Preliminary data from subjects with metastatic pancreatic cancer subjects is presented.

For further information about RX-3117 and Rexahn Pharmaceuticals
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Phase 1 Dose-escalation Summary

- Forty-two subjects were enrolled and treated with various doses and schedules of single agent oral RX-3117 (J Clin Oncol 34, 2016 (suppl; abstr 2555)).
- Increasing doses of RX-3117 were administered to determine safety and tolerability and identify a MTD or RP2D in adults with advanced solid tumors for whom standard therapies have failed or for which no current therapy is available. Thirty-seven subjects had received 4 or more prior cancer treatments RX-3117 was administered:
  - From 30 mg up to 2000 mg, were given every other day (i.e., 3 times a week) for 3 weeks, with 1 week off in each 4-week cycle
  - 500 and 700 mg were administered for 5 consecutive days with 2 days off per week for 3 weeks, with 1 week off in each 4-week cycle
  - 500 mg administered 7 times a week for 3 weeks (21 days continuously), with one week off in each 4-week cycle
- The MTD/RP2D was determined to be: **700 mg administered for 5 consecutive days with 2 days off per week for 3 weeks, with 1 week off in each 4-week cycle.**
- Two dose limiting toxicities were observed: Grade 3 anemia at the 2000 mg dose administered 3 times per week and Grade 3 oral mucositis at 500 mg administered 7 times per week. Both events were reversible.
- 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. Sixteen subjects had stable disease as the best overall response.
- Non-compartmental PK analysis showed that at the RP2D, RX-3117 is absorbed rapidly (Tmax of 3 hrs), providing a maximum plasma concentration of ~1000 ng/mL, and Day 1 AUC of 8600 ng.hr/mL. RX-3117 was eliminated with a half-life of 9 hrs, making RX-3117 ideal for daily dosing.

Phase 1b/2a Pancreatic Subjects Demographics and Safety Profile

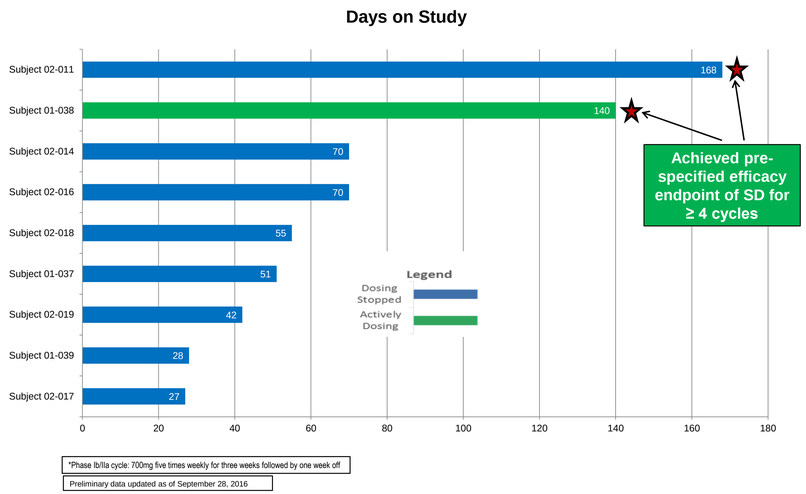
Stage 1 of Phase 1b/2a: Demographics

Total Recruited to date	8
Gender, n (%)	
Female	4 (50%)
Male	4 (50%)
Median age (range)	70 (56-78)
Race, n (%)	
White	7 (89.9%)
Black	1 (11.1%)
ECOG performance status, n (%)	
0	0 (0%)
1	8 (100%)
Number of prior anticancer treatments, n (%)	
1	1 (12.5%)
2	1 (12.5%)
3	1 (12.5%)
4+	5 (62.5%)

Stage 1 of Phase 1b/2a: Safety

Adverse Event	Subjects (N) per severity grade			
	Grade 1	Grade 2	Grade 3/4	Overall
ALT elevated	1	1		2
Anemia		1	1/0	2
AST increased	1	1		2
Decreased appetite	1			1
Diarrhea	2	1		3
Fatigue	2			2
GI Pain	1			1
Hypophosphatemia			1/0	1
Leucopenia		2	1/0	3
Light Headed	1			1
Neutropenia	1	1		2
Thrombocytopenia		1	1/0	2
Vomiting	1			1

Treatment (Days) and Best Overall Response



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.
- Subjects enrolled into stage 1 of the clinical trial had actively progressing disease, with 88% of them having failed ≥ 4 prior cancer therapies (including 5-FU and gemcitabine-based therapies).
- RX-3117 was shown to be safe and well tolerated.
- Two subjects met the predefined protocol efficacy criteria by having progression free survival for more than 4 months.
- Forty additional subjects are now being recruited in stage 2 of the Phase 1b/2a.
- Future clinical studies include combination of RX-3117 with other agents for the treatment of pancreatic and bladder cancer.

Author Disclosures

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