RX3117: Activity of an Oral Antimetabolite Nucleoside in Subjects with Pancreatic Cancer – Preliminary Results of Stage II of the Phase Ia/IIb Study

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Abstract #396

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. Data from stage 2 of the Phase 1b/2a clinical study of RX3117 as a single agent in subjects with metastatic pancreatic cancer is described below.

Methods: Stage 2 of the Phase 1b/2a study (NCT02030067) is designed to evaluate safety, tolerability and efficacy following treatment with 700 mg administered orally once-daily for 5 consecutive days with 2 days off per week for 3 weeks with 1 week off in each 4 week cycle. Eligible subjects (aged ≥ 18 years) had relapsed/refractory metastatic pancreatic cancer. The primary endpoint is a ≥ 20% rate of progression free survival (PFS) benefit (i.e., proportion of subjects with stable disease for at least 4 months) and/or a 10% of evaluable subjects with a partial response rate or better.

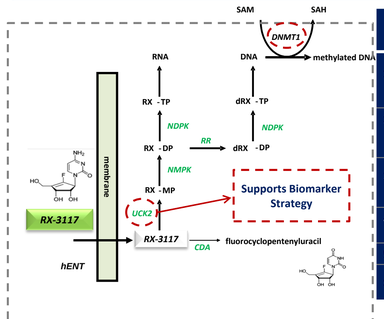
Results: As of Sep 2017, 44 subjects have been enrolled (22 females, 22 males). The median age was 68 years, ECOG performance statuses were 0 (13 subjects) and 1 (31 subjects) and 6 subjects had received 4 or more prior therapies. One subject had an unconfirmed partial response and 21 subjects met the primary endpoint of stable disease with a duration of 30-224 days. The most frequent adverse events were mild to moderate anemia (19%), mild to moderate fatigue (15%), mild to moderate diarrhea (11%), and severe anemia (9%).

Conclusions: This ongoing trial shows an early efficacy signal where RX-3117 is active against advanced pancreatic cancer. The study continues to enroll subjects with advanced pancreatic cancer into stage 2. A phase 2 study with nab-paclitaxel in first-line patients with advanced pancreatic cancer has been started.

Introduction

The therapeutic options for advanced, metastatic pancreatic cancer are very limited. First and second line therapies are chemotherapy-based (i.e. 5-FU and/or gemcitabine combinations). Patients receiving single agent gemcitabine as 1st line therapy for metastatic pancreatic cancer had a progression free survival of 3.7 months (Von Hoff, 2013 NEJM 369: 1691). The recommendation for 3rd line treatment is palliative care or clinical trial. Only 15-20% of metastatic pancreatic patients in the US receive 3rd-line therapy and this is even lower in Europe due to poor performance status and lack of effective and safe therapies. Checkpoint inhibitors are not effective. Disease control with 3rd line therapy is poor with most patients progressing during the first cycle, and disease control at 8 weeks is less than 20% (limited data).

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 Phase 1 study was amended adding a Phase 2a cohort to treat subjects with metastatic pancreatic cancer at the recommended Phase 2 dose identified.

The Phase 2a study uses a 2-stage design. Stage 1 was planned to treat 10 evaluable subjects with metastatic pancreatic cancer. An interim analysis was completed after enrollment of 10 response evaluable subjects (with a minimum of 4 cycles of therapy or early treatment discontinuation due to disease progression). The criteria to proceed to stage 2 was defined as: 20% or more subjects progression free after ≥ 4 cycles of treatment or a partial/complete response in at least 10% of subjects. Since the criteria were met, Stage 2 was opened and 45 patients were enrolled.

Data was updated as of Dec 2017, 45 subjects (Stages 1 and 2) and 1 subject from the dose expansion are reported.

Demographics*

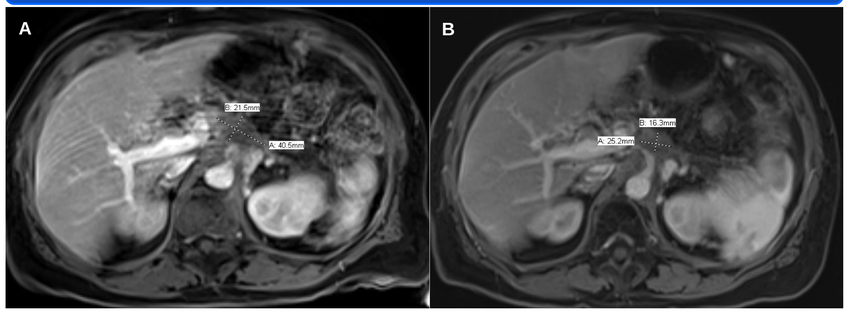
Category		Category	
Gender	n (%)	ECOG score	n (%)
Female	24 (52%)	0	15 (33%)
Male	22 (48%)	1	31 (67%)
		Median age (range)	69 (52-86)
Race	n (%)	Prior anticancer treatments	n (%)
White	33 (71.7%)	1	10 (22%)
Black	4 (8.7%)	2	19 (41%)
Asian	2 (4.4%)	3	11 (24%)
Other	3 (6.5%)	4+	6 (13%)
Undeclared	4 (8.7%)	Prior gemcitabine	43 (93%)

*Includes 1 subject from the dose expansion who also met the efficacy criteria

Phase 2 Pancreatic Safety Profile

AE	Grade 1/2	Grade 3/4
Anemia	16 (17%)	8 (9%)
Fatigue	13 (14%)	1 (1%)
Diarrhea	12 (13%)	1 (1%)
Nausea	7 (7%)	0
Leukopenia	6 (6%)	1 (1%)
Neutropenia	4 (4%)	0
Thrombocytopenia	3 (3%)	0
Elevated ALT	3 (3%)	0

Results



Subject 12-007 was initially treated with gemcitabine and cisplatin for 3 months, gemcitabine and Abraxane™ for 1 month, and FOLFIRI for 9 months. The subject progressed on all therapies. One month of treatment with RX-3117 resulted in an unconfirmed PR of the pancreatic body and lung – left lower lobe. Baseline image of the pancreatic body mass is shown in A and the pancreatic body mass following 1 month of study treatment is shown in B.

- Of the 46 patients enrolled, 43 patients were response evaluable
- In the response evaluable population:
  - 40/43 (93%) previously received gemcitabine
  - Patients were treated with an average of 2.4 cancer therapies (1-5)
    - 37% failed ≥ 3 prior cancer therapies
  - Disease control at 8 weeks was 31% (0 Complete Response/1 Partial Response/12 Stable Disease)
    - 5 patients had stable disease for more than 4 months
    - No significant changes on CA 19.9

Conclusions

- RX-3117 appears safe and well tolerated when administered at the recommended Phase 2 dose of 700 mg for 5 consecutive days with 2 days off per week for 3 weeks with 1 week off in each 4 week cycle to subjects with advanced metastatic pancreatic cancer.
- These preliminary results showed encouraging data since RX-3117 treatment of heavily pretreated pancreatic cancer patients demonstrated superior disease control than single agent gemcitabine treatment in first line setting (31% vs <20%).
- A Phase 2 study that combines RX-3117 with nab-paclitaxel in first-line advanced metastatic pancreatic cancer patients is currently ongoing.

Author Disclosures

Julie Poore, and Ely Benaim, MD – Rexahn Pharmaceuticals

For further information about RX-3117 and Rexahn Pharmaceuticals
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