RX-3117, an Oral Hypomethylating Agent to Treat Advanced Solid Tumors (ST): Interim results from an Ongoing Phase 2a Study in Advanced Urothelial Cancer (aUC)

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Abstract #501

Background: RX-3117 is an oral small molecule hypomethylating agent, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117 shows efficacy in various xenograft models, including those of gemcitabine resistant bladder cancer. Preliminary data from Stage 2 of a Phase 2a clinical study of RX-3117 as a single agent in subjects with aUC is described below.

Methods: This Phase 2a study (2-stage design, NCT02030067) evaluates the efficacy of RX-3117 in eligible patients (aged ≥ 18 years) with refractory aUC. Primary objectives include safety and efficacy of the recommended Phase 2 dose and schedule identified in the Phase 1 portion of the study. Patients received 700 mg of oral RX-3117 daily for either 3 weeks with 1 week off in each 4-week cycle or 4 continuous weeks. The primary endpoint is a ≥ 20% rate of progression free survival benefit (i.e., proportion of patients with stable disease for at least 4 months) and/or a 10% of evaluable patients with a partial response or better.

Results: As of October 2017, 17 patients (12 males, 5 females) with aUC were treated with RX-3117. The median age was 66 years, ECOG performance status was 0 to 1 and 53% received ≥ 3 prior therapies. Metastatic disease sites included lung, liver, lymph nodes, and mediastinum. Four patients achieved stable disease for 4 cycles of RX-3117 treatment; one patient received treatment for 168 days and another patient for 301 days. One patient showed tumor shrinkage as measured by RECIST (-15.5%) after 4 cycles of RX-3117; another patient showed a 19% tumor reduction after 1 cycle. The most frequent related adverse events were G1 diarrhea (13%), fatigue (13%), nausea (10%), G1/G2 anemia (10%), vomiting (10%) and G3 thrombocytopenia (10%).

Conclusions: RX-3117 is safe and well tolerable and shows preliminary evidence of anti-tumor activity. The study continues to enroll patients with aUC in Stage 2.

Introduction

Currently, first line therapy for aUC is commonly combination gemcitabine and cisplatin. Despite the clinical value of gemcitabine, drug resistance is common, which may be due to reduced prodrug phosphorylation by deoxycytidine kinase (dCK). RX-3117 is alternatively phosphorylated by uridine-cytidine kinase 2 (UCK2), an enzyme found in cancer cells. RX-3117 is inactivated by cytidine deaminase at a slow rate, allowing higher cellular concentrations. Both features are expected to enhance RX-3117 anticancer activity. Within the last 15 years, PD-1 inhibitors are the only new treatments approved for aUC as second line therapy. No third line treatment is approved other than supportive care. While some patients get a prolonged durable response to PD-1 inhibitors, the vast majority (70-80%) progress and may benefit from additional therapeutic options such as RX-3117.

Study Design

The ongoing Phase 2a study uses a 2-stage design. Stage 1 planned to treat 10 subjects with advanced urothelial 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 continues to enroll patients. Preliminary data was updated as of January 2018, 27 subjects, from Stages 1 and 2, are reported.

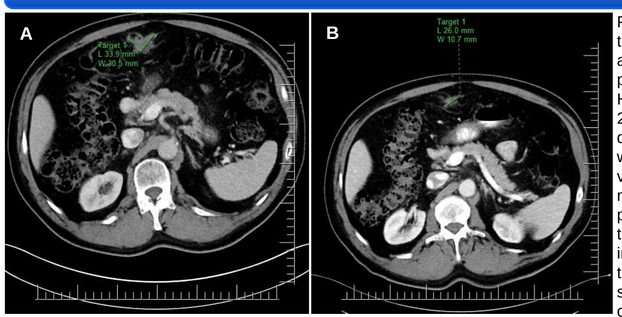
Demographics

Gender	n (%)	ECOG score	n (%)
Female	8 (30%)	0	10 (37%)
Male	19 (70%)	1	17 (63%)
Race	**n (%)**	**Prior anticancer treatments**	**n (%)**
White	24 (88%)	1	3 (11%)
Black	1 (4%)	2	8 (30%)
Asian	1 (4%)	3	13 (48%)
Other	1 (4%)	4+	3 (11%)
		Prior Gemcitabine	23 (85%)
Age	**Median (Range)**	Prior Immunotherapy	18 (67%)
	67 (48-84)	Prior Cisplatin	14 (52%)

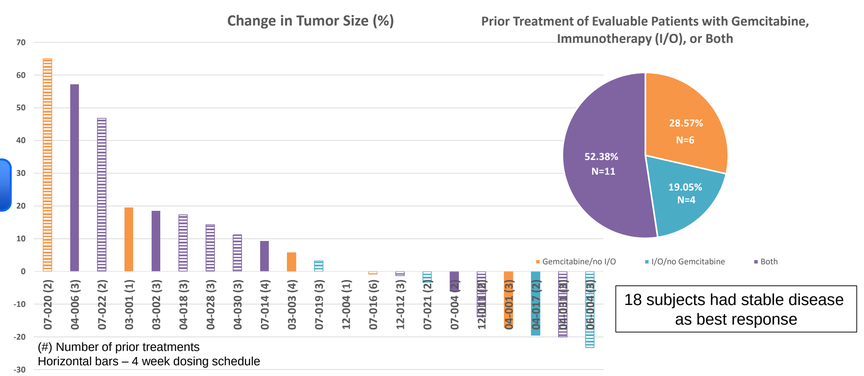
Safety Profile

Related AE	Grade 1/2	Grade 3/4
Diarrhea	8 (14%)	0
Fatigue	5 (9%)	0
Nausea	5 (9%)	0
Vomiting	5 (9%)	0
Anemia	4 (7%)	2 (4%)
Leukopenia	2 (4%)	3 (5%)
Neutropenia	2 (4%)	1 (2%)
Thrombocytopenia	1 (2%)	4 (7%)
Abdominal Pain	2 (4%)	1 (2%)

Results

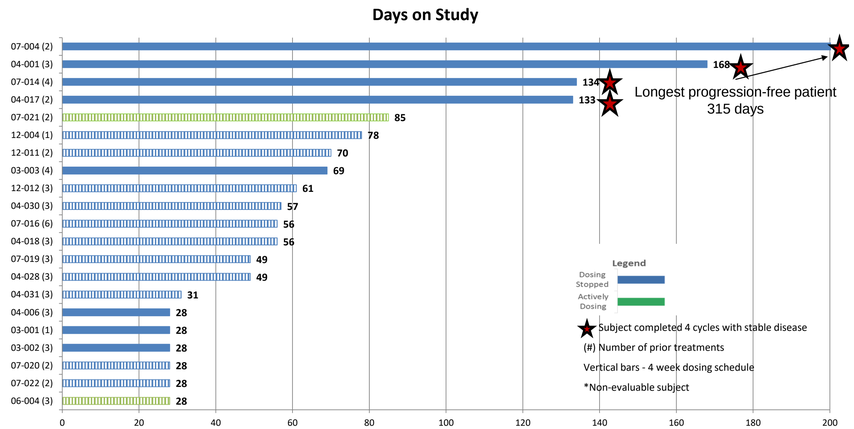


Patient 06-004 was initially treated with MVAC for 4 months and completed therapy. The patient was treated with Herceptin® and pertuzumab for 25 months and discontinued dur to disease progression. The patient was treated with an oncolytic virus and pembrolizumab for 3 months, and after which progressed. One month of treatment with RX-3117 resulted in a tumor reduction of 23.3% in the peritoneum. Baseline image shown in A and image after 1 cycle is shown in B.



18 subjects had stable disease as best response

Results



- In the response evaluable population (21 patients):
  - Patients were treated with an average of 2.7 cancer therapies (range 1-6)
    - 57% of patients failed ≥ 3 prior cancer therapies
  - Disease control at 8 weeks was 33% (0 Complete Response/0 Partial Response/7 Stable Disease)
    - 4 patients had stable disease for more than 4 months

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 for 4 weeks in each 4 week cycle to subjects with aUC.
- These preliminary results show encouraging responses in heavily pretreated patients.
- The study continues to enroll patients with aUC in Stage 2 at 4 continuous weeks of dosing.

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For further information about RX-3117 and Rexahn Pharmaceuticals
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