Preliminary Results From an Ongoing Phase 2a Study of RX-3117, an Oral Nucleoside Analogue to Treat Advanced Urothelial Cancer (aUC)

Jacob J. Adashek[1], Sumanta K. Pal[1], Vincent M. Chung[1], Scott T. Tagawa[2], Joel Picus[3], Hani M. Babiker[4], Sumati Gupta[5], Raymond Wadlow[6] Julie Poore[7], Christine Peterson[7], and Ely Benaim[7];

[1]City of Hope, Duarte, CA; [2]Weill Cornell Medical College, New York, NY; [3]Washington University in St. Louis School of Medicine, St. Louis, MO; [4]University of Arizona Cancer Center, Tucson, AZ; [5]University of Utah Huntsman Cancer Institute, Salt Lake City, UT; [6]Virginia Cancer Specialists, Fairfax, VA; [7]Rexahn Pharmaceuticals Inc., Rockville, MD

Abstract #4543

Background: RX-3117 is an oral small molecule nucleoside analogue (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 advanced urothelial cancer (aUC) is described below. **Methods:** The efficacy of oral RX-3117 was evaluated in eligible patients (aged ≥ 18 years) with refractory aUC in a Phase 2a study. Primary objectives include safety and efficacy of 700 mg of RX-3117 administered orally for 5 consecutive days followed by 2 days off per week in each 4-week cycle for 4 continuous weeks. 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 10% of evaluable patients with a partial or better response by RECIST criteria. **Results:** As of February 2018, 27 patients (19 males, 8 females) with aUC were treated with RX-3117. The median age was 67 years and ECOG performance status was ≤ 1. Prior treatment with gemcitabine or immunotherapy was 85% or 67% of patients, respectively. Five patients achieved stable disease for 4 cycles of RX-3117 treatment; one patient received treatment for 315 days and another patient continues treatment beyond 4 months. One patient achieved a partial response after 2 cycles. Four patients have shown a tumor reduction ranging from 13.9 to 20% as measured by RECIST. All reductions occurred after 1 cycle of RX-3117 treatment, except for one patient's reduction, which occurred after 4 cycles. The most frequent related adverse events were G1/2 diarrhea (14%), fatigue (9%), nausea (9%), vomiting (9%), G1/G2 anemia (7%), and G3 thrombocytopenia (7%). **Conclusions:** RX-3117 is safe and well tolerated and shows preliminary evidence of anti-tumor activity in heavily pretreated patients. The study continues to enroll subjects with aUC in Stage 2.

Introduction

Currently, first line therapy for aUC is commonly combination gemcitabine and cisplatin, with pembrolizumab and atezolizumab approved for cisplatin-ineligible patients. 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 patients with advanced urothelial cancer. An interim analysis was completed after enrollment of 10 response evaluable patients (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 patients progression free after ≥ 4 cycles of treatment or a partial response (PR)/complete response (CR) in at least 10% of patients. Since the criteria were met, Stage 2 was opened. The recommended Phase 2 dose is 700mg for 5 consecutive days with 2 days off for 4 weeks in each 4 week cycle. Preliminary data was updated as of May 2018, 29 enrolled patients, from Stages 1 and 2, are reported.

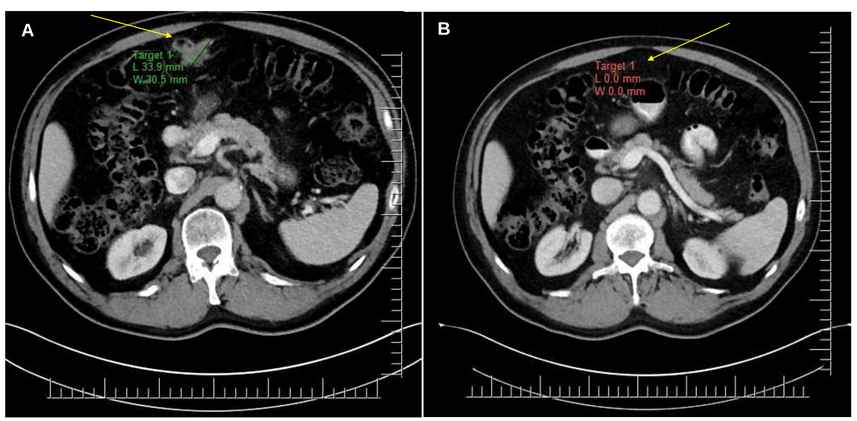
Demographics

Gender	n (%)	ECOG score	n (%)
Female	8 (28%)	0	11 (38%)
Male	21 (72%)	1	18 (62%)
Race	**n (%)**	**Prior Anticancer Treatments**	**n (%)**
White	26 (90%)	1	3 (10%)
Black	1 (3.3%)	2	8 (28%)
Asian	1 (3.3%)	3	13 (45%)
Other	1 (3.3%)	4+	5 (17%)
		Prior Gemcitabine	24 (83%)
Age	**Median (Range)**	Prior Immunotherapy	20 (69%)
	67 (48-84)	Prior Cisplatin	15 (52%)

Safety Profile

AE	Grade 1/2	Grade 3/4
Fatigue	11 (13%)	
Diarrhea	8 (10%)	
Nausea	6 (7%)	
Vomiting	6 (7%)	
Anemia	6 (7%)	3 (4%)
Abdominal Pain	3 (4%)	1 (1%)
Leukopenia	3 (4%)	3 (4%)
Pruritis	3 (4%)	
Neutropenia	2 (2%)	2 (2%)
Thrombocytopenia	2 (2%)	4 (5%)
Anorexia	2 (2%)	

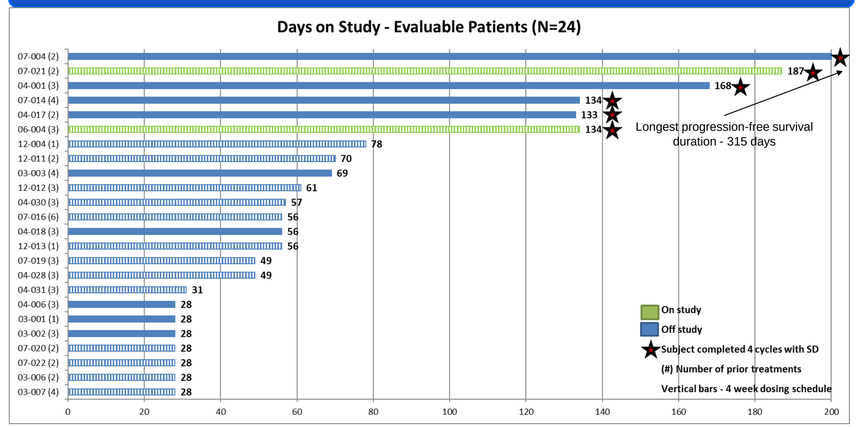
Results

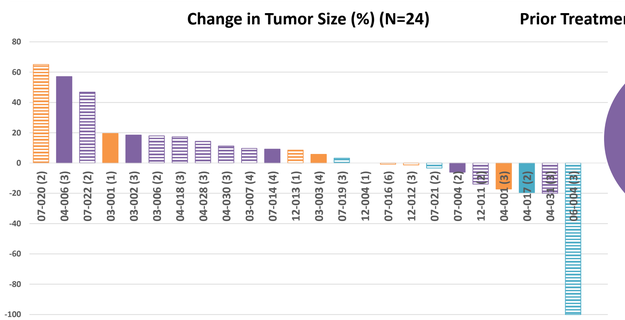


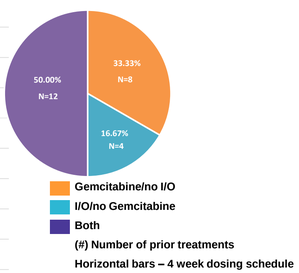
Patient 06-004 was initially treated with MVAC for 4 months and completed therapy. The patient was treated with trastuzumab and pertuzumab for 25 months and discontinued due to disease progression. The patient was treated with an oncolytic virus and pembrolizumab for 3 months, and after which the patient progressed. Four months of treatment with RX-3117 resulted in CR in the peritoneum. The patient had a PR after two and three months of treatment. Baseline image shown in A and image after 4 cycles is shown in B. The patient is currently in Cycle 6 of treatment and has not experienced any SAEs or Grade 3/4 AEs.

For further information about RX-3117 and Rexahn Pharmaceuticals
please contact Dr. Ely Benaim: benaime@rexahn.com, (240) 268-5300 x 304

Results







Conclusions

- These preliminary results show encouraging responses in heavily pretreated patients.
  - Of 24 evaluable patients, 25% had disease control at 4 months.
    - 1 complete response (CR)
    - 5 patients with stable disease (SD)
      - 1 patient with SD at 10 months
      - 1 patient with SD at 6 months
  - Over half (54%) of patients failed ≥ 3 prior cancer therapies.
  - Patients were treated with an average of 2.7 prior cancer therapies with a range of 1-6.
- RX-3117 appears safe and well tolerated when administered at the recommended Phase 2 dose to patients with aUC.
- The study continues to enroll patients with aUC in Stage 2.