Activity of RX-3117, an Oral Antimetabolite Nucleoside, in Subjects with Advanced Urothelial Cancer: Preliminary Results from a Phase IIa Study

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Abstract #455

Background: RX-3117 is an oral small molecule antimetabolite that is activated by uridine cytidine kinase 2 (UCK2) which is predominantly expressed in cancer cells. RX-3117 has shown efficacy in xenograft models of gemcitabine resistant pancreatic, bladder and colorectal cancer. Preliminary data from an analysis of a Phase 2a clinical study of RX3117 in advanced urothelial cancer is described.

Methods: In the Phase 2a study designed to evaluate safety, tolerability and efficacy, subjects were treated with oral RX-3117 (700 mg) once-daily for 5 consecutive days on and 2 days off for 3 of 4 weeks or all 4 weeks in a 28-day cycle. Eligible subjects (aged ≥ 18 years) had relapsed/refractory metastatic urothelial cancer, ECOG PS of 0 to 1, normal organ function (hepatic, renal and hematology) with no limit on the number of prior therapies. The primary Phase 2a endpoints are progression free survival (PFS) and/or objective clinical response with secondary endpoints of safety, TTP, DOR and ORR.

Results: As of October 5, 2018; 33 subjects were treated (23 males and 10 females, median age 67.5 years); 29 subjects were evaluable having completed more than 1 cycle of therapy or discontinued due to a related adverse event. Twenty subjects had received 3 or more prior therapies; 30 received gemcitabine/cisplatin and 25 received a checkpoint inhibitor. The most common related adverse events were anemia (G1-2%, G2-3%, G3-3%), fatigue (G1-6%, G2-3%), neutropenia (G2-2%, G3-5%, G4-2%), diarrhea (G1-4%, G2-2%), and thrombocytopenia (G2-2%, G3-3%, G4-1%). One subject had a complete response after 4 cycles of therapy and continues therapy beyond 10 cycles; 5 subjects had PFS ranging from 133 to 315 days.

Conclusions: RX-3117 appears to be safe and well-tolerated in chemotherapy and immunotherapy refractory advanced urothelial cancer with acceptable toxicities. Preliminary results show anti-tumor activity in heavily pre-treated patients. (NCT02030067)

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

Phase 2 Design: The ongoing Phase 2a study uses a 2-stage design. Stage 1 was completed following an interim analysis of 10 response evaluable patients (with a minimum of 4 cycles of therapy or early treatment discontinuation due to disease progression). Stage 2 began when the criteria of 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 was met. Preliminary data, updated as of January 2019, are reported from Stages 1 and 2. Of the 35 patients enrolled, 31 were evaluable.

Treatment: The recommended Phase 2 dose is 700mg for 5 consecutive days with 2 days off for 3 of 4 weeks or all 4 weeks in a 28-day cycle.

Phase 2 Primary Objective:

- To investigate the antitumor activity of RX-3117 in subjects with aUC

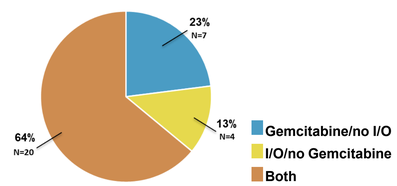
Phase 2 Secondary Objectives:

- To assess additional measures of antitumor activity
- To characterize the safety profile associated with RX-3117
- To evaluate population pharmacokinetics using a limited sampling

Baseline Characteristics

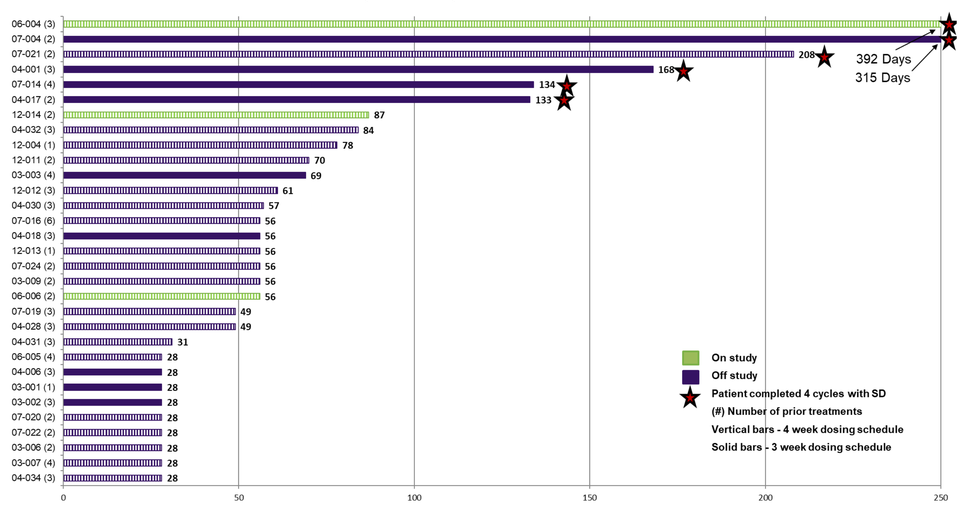
Gender - no. (%)		ECOG - score no. (%)	
Female	11 (31)	0	12 (34)
Male	24 (69)	1	23 (66)
Race - no. (%)		**Prior Anticancer Treatments - no. (%)**	
White	31 (89)	1	3 (9)
Black	3 (8)	2	13 (37)
Asian	1 (3)	3	13 (37)
Other	0 (0)	4+	6 (17)
Age (Years)		Gemcitabine	31 (89)
Median	67	Immunotherapy	27 (77)
Range	48-84	Cisplatin	19 (54)

Prior Treatment: Evaluable Patients



Results

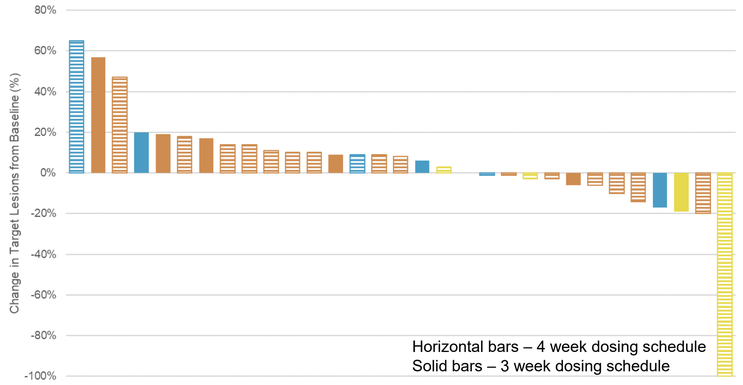
Days on Study: Evaluable Patients

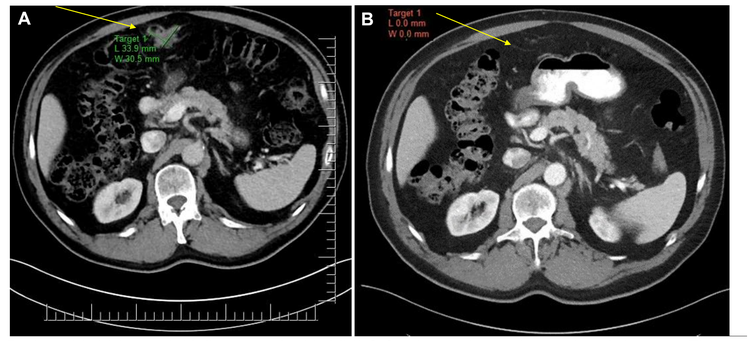


Safety

Related AE	Grade 1/2 - no. (%)	Grade 3/4 - no. (%)
Fatigue	16 (12)	
Diarrhea	14 (10)	
Anemia	7 (5)	5 (4)
Thrombocytopenia	3 (2)	7 (5)
Neutropenia	3 (2)	6 (4)
Nausea	8 (6)	
Vomiting	7 (5)	
Leukopenia	3 (2)	4 (3)
Abdominal Pain	3 (2)	1 (1)
Pruritis	4 (3)	

Best Overall Response per Patient





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. Baseline image shown in A and image after 14 cycles is shown in B. The patient is currently in Cycle 15 of treatment with no long-term hematologic effects observed.

Conclusions

- These preliminary results show encouraging responses in heavily pretreated patients.
  - Of 31 evaluable patients, 19% had disease control at 4 months.
    - 1 complete response (CR) with patient continuing treatment after 14 months
    - 5 patients with stable disease (SD) ≥ 4 months
      - 1 patient with SD at 10 months
      - 1 patient with SD at 6 months
  - Over half (54%) of patients failed ≥ 3 prior cancer therapies.
- RX-3117 appears safe and well tolerated when administered at the recommended Phase 2 dose to patients with aUC.

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