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 hematological) 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): 25 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; 90 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%, G2-2%, 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. (NCT02030068)

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 produg 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 antitumor activity. Within the last 15 years, PD-1 inhibitors are the only new treatments approved for metastatic urothelial cancer, ECOG PS of 0 to 1, normal organ function (hepatic, renal and hematological) 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.

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 2, 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 on and 2 days off for 3 of 4 weeks or all 4 weeks in a 28-day cycle.

Phase 2a Primary 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

 methods and results
These preliminary results show encouraging responses in heavily pretreated patients.
• 31 evaluable patients, 19% had disease control after 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
• 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.