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

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Abstract # 873P

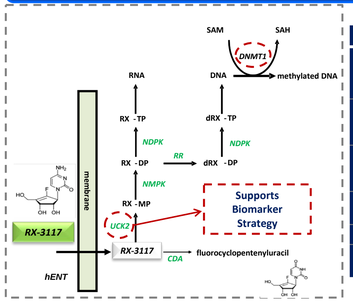
Background RX-3117 is an oral small-molecule hypomethylating agent, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117 shows efficacy in various xenograft models, including those of gemcitabine resistant bladder and colorectal cancers. Data from the stage 1 of a Phase 2a clinical study of RX-3117 as a single agent in subjects with advanced urothelial cancer are described below.

Methods This Phase 2a study with a 2-stage design (NCT02030067) evaluates the efficacy of RX-3117 in eligible subjects (aged ≥ 18 years) with advanced urothelial cancer previously treated with an unlimited number of prior therapies. Primary objectives include safety and efficacy of the recommended Phase 2 dose (RP2D) and schedule identified in the Phase 1 portion of the study. Subjects received 700 mg of oral RX-3117 daily for 3 weeks with 1 week of rest in each 4 week cycle. The response criteria of complete response or partial response in 1 or more subjects or stable disease for 4 cycles in 2 or more subjects in Stage 1 in order to proceed to Stage 2.

Results As of May 2017, 10 subjects with advanced urothelial cancer were treated with RX-3117 (4 females, 6 males). Of those 10 subjects, 70% received ≥ 3 prior therapies, had performance score of 0-1 and multiple disease sites (lung, liver, lymph nodes and pelvis). Two subjects met the protocol defined response criteria of stable disease for 4 cycles of RX-3117 treatment; one subject received treatment for 168 days and another subject continues receiving therapy (147 days at abstract submission). In addition, 1 subject showed tumor shrinkage as measured by RECIST (-15%); another subject still on treatment showed a 19% tumor reduction after 2 cycles of RX-3117. Related adverse events were G2 anemia, G1 anorexia, G1 epistaxis, G1 fatigue, G1 nausea, G1 diarrhea, G1/G2 vomiting, G2 mucositis, G3 leukopenia, G1/G3 neutropenia, and G3 thrombocytopenia. One subject had a treatment delay and dose reduction.

Conclusions Single agent RX-3117 appears to be safe and well tolerated and shows evidence of preliminary tumor activity. The predefined efficacy criteria was met in Stage 1, and Stage 2 is ongoing. Results from Stage 1 of the phase 2a will be presented.

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 to add a Phase 2a study to treat subjects with metastatic urothelial cancer with single agent RX-3117 at the recommended Phase 2 dose identified in Phase 1.

The Phase 2a study uses a 2-stage design. Stage 1 was planned to treat 10 evaluable subjects with metastatic urothelial cancer. An interim analysis was conducted after enrollment of 10 subjects evaluable for response (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 enrollment is continuing.

The 10 stage 1 subjects from the abstract are reported as well as additional subject enrolled in the Phase 2a study.

For further information about RX-3117 and Rexahn Pharmaceuticals
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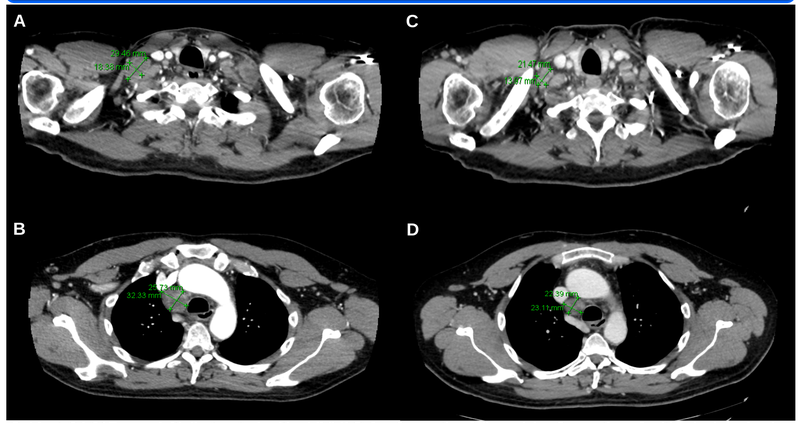
Demographics

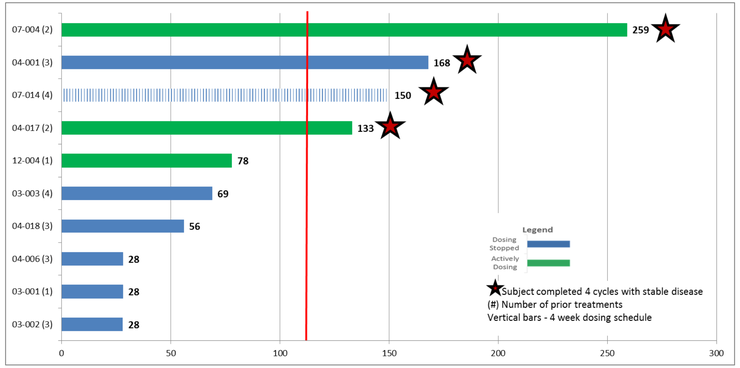
Category		Category	
Gender	n (%)	ECOG score	n (%)
Female	4 (40%)	0	1 (10%)
Male	6 (60%)	1	9 (90%)
Race	n (%)	Median age (range)	62 (49-84)
White	9 (90%)		
African American	1 (10%)		
Most Common Metastatic Sites		Number of Prior Anticancer Treatments	n (%)
Lung		1	2 (20%)
Lymph Nodes		2	2 (20%)
Liver		3	4 (40%)
Mediastinum		4+	2 (20%)
		(9/10 subjects received prior gem)	

Tumor Reduction



Subject 04-017 was initially treated with ddMVAC for 6 months followed by 3 months of with nivolumab plus ipilimumab; subject progressed on both therapies. One month post-immunotherapy, treatment with RX-3117 resulted in reductions in tumor volume of bulky right supraclavicular and paratracheal superior mediastinal lymph nodes. Baseline images of right supraclavicular and paratracheal superior mediastinal lymph nodes are shown in A and B, respectively, and corresponding lesions following 3 months of study treatment are shown in C and D, respectively.

Days on Study



Related Adverse Events (AE)

	Subjects N=10 n (%)	
AE	Grade 1-2	Grade 3
Any AE	7 (70%)	2 (20%)
Diarrhea	3 (30%)	0
Fatigue	3 (30%)	0
Anemia	2 (20%)	0
Aches	1 (10%)	0
Anorexia	1 (10%)	0
Arthralgias	1 (10%)	0
Mucositis	1 (10%)	0
Nausea	1 (10%)	0
Vomiting	1 (10%)	0
Neutropenia	0	1 (10%)
Leukopenia	0	1 (10%)
Thrombocytopenia	0	1 (10%)

Conclusions

- RX-3117 is safe and well tolerated when administered at the recommended Phase 2 Dose of 700 mg in a population of heavily pretreated subjects with advanced urothelial cancer.
- 60% of subjects enrolled in the current clinical trial had received 3 or more lines of therapy, including different chemotherapy combinations.
- Four subjects (40%) met the pre-defined protocol efficacy criteria of stable disease after 4 cycles of treatment.
- Additional subjects are enrolling in Stage 2 of the Phase 1b/2a.
- Future clinical studies include combining RX-3117 with other agents for the treatment of advanced urothelial cancer.

Author Disclosures

Julie Poore, Christine Peterson, PhD, and Ely Benaim, MD – Rexahn Pharmaceuticals