Activity of RX-3117, an oral antimetabolite nucleoside, in subjects with metastatic bladder cancer resistant to gemcitabine: Preliminary results of a phase Ib/IIa study

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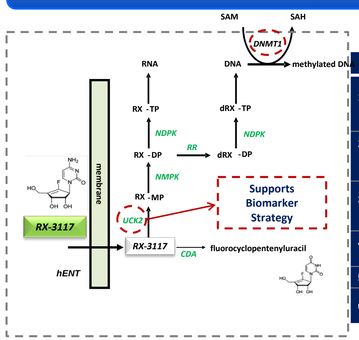
Abstract #445

Background: RX-3117 is an oral small molecule antimetabolite, cyclopentyl pyrimidyl nucleoside that is activated by uridine cytidine kinase 2. RX-3117 has shown efficacy in xenograft models of gemcitabine resistant pancreatic, bladder and colorectal cancer. Preliminary data from an analysis of a phase 1b/2a clinical study of RX3117 in metastatic bladder cancer is described.
Methods: This phase 1b/2a study (NCT02030067) was designed to evaluate safety, tolerability and efficacy following treatment with 700 mg administered orally once-daily for 5 consecutive days with 2 days off per week for 3 weeks with 1 week off in each 4 week cycle in a 2-stage design. Eligible subjects (aged ≥ 18 years) were those with relapsed/refractory metastatic bladder cancer with any number of prior therapies. Prior therapy with platinum-based chemotherapy was required. The primary endpoint was to assess the efficacy and safety of RX-3117 in metastatic bladder cancer, with secondary aims of evaluating PFS and CBR.
Results: With 9 subjects enrolled, median age was 66 years, ECOG PS was 0-1. All subjects had received gemcitabine/cisplatin in the perioperative or metastatic setting, and 4 subjects had received 3 or more prior therapies. The most frequent related adverse events were anemia, mild-moderate fatigue, vomiting and diarrhea. No dose limiting toxicities were observed. PFS and CBR will be presented at the meeting, as 5 subjects continue to receive therapy at the time of this submission. One subject continues on treatment at 139 days with persistent stable disease. Molecular profiling of his bladder tumor showed alterations in ARID1A, FBSW7, FGFR3, NF1, and TERT. The patient previously responded to an FGFR3 inhibitor but progressed after 9 months, with ctDNA assessments showing incurrence of TP53 alteration. Clinical benefit with RX-3117 was achieved in spite of incurrence of this alteration.
Conclusions: RX-3117 demonstrated an excellent safety profile, and prolonged stable disease was seen in 1 subject who failed prior cisplatin/gemcitabine and FGFR3 inhibition. Activity persisted despite development of a putative resistance alteration detected by ctDNA.

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

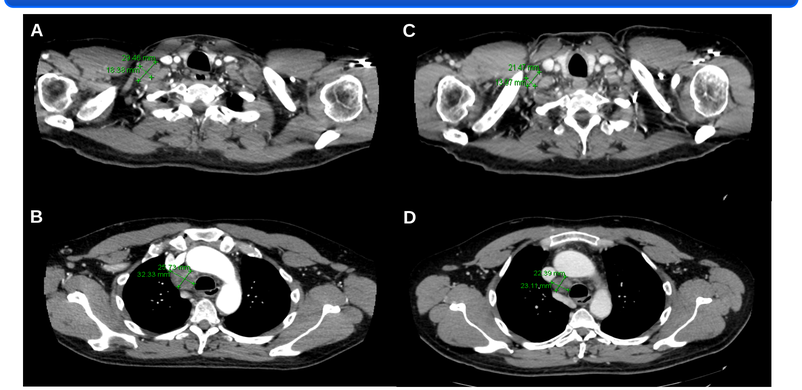
Study Design

The Phase 1 study was amended to allow a 2-stage phase 1b/2a study design to treat subjects with metastatic bladder cancer with single agent RX-3117 at the dose and schedule identified in Phase 1.
Stage 1 was planned to treat 10 evaluable subjects with metastatic bladder cancer.
Advancement to stage 2 was predefined as 20% or more subjects with progression free survival of ≥ 4 cycles of treatment or a partial/ complete response in at least 10% of subjects.

Stage 1 of Phase 2 Demographics

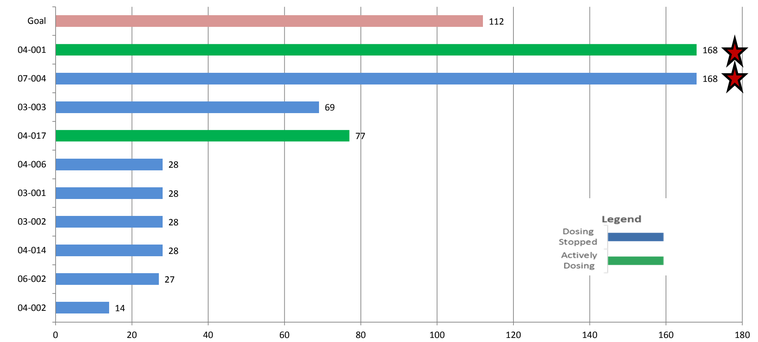
Category		Category	
Gender	n (%)	ECOG score	n (%)
Female	4 (40%)	0	2 (20%)
Male	6 (60%)	1	8 (80%)
Race	n (%)	Median age (range)	63 (49-83)
White	10 (100%)		
Common Disease Sites		Prior anticancer treatments	n (%)
Bladder		1	1 (10%)
Lung		2	2 (20%)
Lymph Nodes		3	6 (60%)
Liver		4+	1 (10%)
Pelvis		(9/10 subjects received prior gem)	
Mediastinum			

Tumor Reduction



Subject 04-017 was initially treated with ddMVAC for 6 months followed by 3 months of with nivolumab with 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 in a patient with prolonged SD who was found to have a putative *TP53*^{R175H} resistance mutation on subsequent ctDNA assessment. 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 Treatment



★ indicates primary endpoint for stage 1 was met

Related Adverse Events

The most frequent adverse events are G1 diarrhea, G1 fatigue, G1 nausea, and G1/G2 vomiting. There were 2 subjects with G3 thrombocytopenia.

Conclusions

- RX-3117 is safe and well tolerated when administered at the recommended Phase 2 Dose of 700 mg administered for 5 consecutive days with 2 days off for 3 weeks with 1 week off.
- Subjects enrolled into stage 1 of the clinical trial had active progressive disease, with 73% of them having failed 3 or more prior cancer therapies (including gemcitabine-based therapies).
- Two subjects met the predefined protocol efficacy criteria by having stable disease for more than 4 months.
- Additional subjects are now being recruited in Stage 2 of the Phase 1b/2a.
- Future clinical studies include combining RX-3117 with other agents for the treatment of bladder cancer.

Author Disclosures

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For further information about RX-3117 and Rexahn Pharmaceuticals
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