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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Background: RX-3117 is an oral small molecule antimetabolite, cyclopentyl pyrimidyl nucleoside that is activated by uridine catalyzed kinase. RX-3117 has shown efficacy in xenograft models of gemcitabine-resistant bladder cancer and clinical data is emerging. This study was designed to evaluate safety, tolerability and efficacy of RX-3117 in metastatic bladder cancer.

Methods: The phase Ib/2a study (NCT02030067) was designed to evaluate safety, tolerability and efficacy of RX-3117 in metastatic bladder cancer. The primary outcome was to assess the efficacy and safety of RX-3117 in metastatic bladder cancer, with secondary aims of evaluating PFS and CBR.

Results: In 9 subjects enrolled, median age was 65 yrs. ECOG PS 0-1. All subjects had received gemcitabine/платино in the perioperative or metastatic setting, and 4 subjects had received 3 or more prior therapies. The most frequent related adverse events were anemia, micromolecule 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 on treatment at 150 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 FGFR3 inhibitor but progressed after 9 months, with concomitant assessments showing inincurrence of TP53 alteration. Clinical benefit with RX-3117 was achieved in spite of inoccurrence 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 resistant alteration identified in Phase 1.

Days on Treatment

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

Related Adverse Events

- 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

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

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

RX-3117 Proposed Mechanism

RX-3117 is a novel oral nucleoside analog that is activated by uridine catalyzed kinase. RX-3117 is an orally bioavailable small molecule with a proven safety profile that demonstrated superior efficacy compared to gemcitabine.

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 at 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

<table>
<thead>
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<th>Category</th>
<th>Value</th>
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<tbody>
<tr>
<td>Gender</td>
<td>n (%)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>ECOG score</td>
<td>n (%)</td>
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<tr>
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<td>2 (20%)</td>
</tr>
<tr>
<td>1</td>
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</tbody>
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Common Disease Sites

- Bladder: 1 (100%)
- Lung: 2 (20%)
- Lymph Nodes: 3 (60%)
- Liver: 4 (100%)
- Pelvis: 9 (910 subjects received prior gem)

Common Disease Sites

- Pelvis (9/10 subjects received prior gem)
- Liver
- Lymph Nodes
- Lung

Clinical Benefit

Subject 04-017 was initially treated with ddI/VAC for 6 months followed by 3 months of 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 supravacular and parastrachal superior medilum lymph nodes in a patient with prolonged SD who was found to have a putative TP53/TH resistance mutation on subsequent ctDNA assessment. Baseline images of right supravacular and parastachal 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.

Tumor Reduction

Days on Treatment

- 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).
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