RX-0201, An Anti-Sense Targeting AKT-1 to Treat Metastatic Renal Cancer - Preliminary Stage 1 Data
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Abstract
Background: RX-0201 is a 20-mer oligonucleotide that is complementary to AKT-1 messenger ribonucleic acid (mRNA). The specificity of RX-0201 mediated effect on AKT-1 mRNA levels was examined in human renal cell carcinoma (von Hippel-Lindau protein-deficient renal cell carcinoma cell line) UMRC2 cells and resulted in a reduction of AKT-1 mRNA levels. In a single agent phase 1 study the maximum tolerated dose of RX-0201 was 250 mg/m²/day. The most frequently reported related adverse events were fatigue, nausea, anorexia and arthralgia.

Methods: The current study is a proof of concept phase 2a, multi-center, open-label study conducted in 2 stages. Stage 1 is an open-label, dose-escalation study of RX-0201 administered in combination with everolimus. RX-0201 will be administered by a 24 hour continuous intravenous infusion for 14 days followed by 7 days of rest. It is expected that 250 mg/m²/day or a lower dose of RX-0201 will be identified as safe and well-tolerated when administered in combination with 10 mg of everolimus. The dose of RX-0201 identified in Stage 1 will be studied further in Stage 2 which is a randomized, open-label, 2-arm study of RX-0201 in combination with 10 mg of everolimus versus 10 mg of everolimus alone in patients with advanced RCC and progression on at least 1 line of VEGF-directed therapy.

Results: To date 2 of the 3 planned RX-0201 escalating doses (125 mg/m²/day, n = 3) and 200 mg/m²/day (n = 3) have been administered as a continuous infusion for 14 days with 10 mg of everolimus administered daily. One subject experienced a 15% lesion reduction and stable disease for 297 days. A second subject had stable disease for 170 days. The most commonly reported adverse events include thrombocytopenia, mouth ulcerations, decreased weight, facial edema, and hyponatremia; no dose limiting toxicities have been reported at this time.

Conclusions: At the dose level tested, RX-0201, in combination with everolimus, appears to be well tolerated. Dose escalation/modification is ongoing to determine the recommended phase 2 dose of RX-0201 when combined with everolimus.

Study Design

Methodology: This study is a 2-stage multi-center, open-label, Phase 2a study to assess the safety and tolerability of Archexin® (RX-0201) in combination with everolimus as monotherapy to treat subjects with advanced renal cell carcinoma treated with the combination of RX-0201 and everolimus versus everolimus alone (Stage 2). The study is randomized, open-label, 2-arm dose expansion study of Archexin® (RX-0201) in combination with everolimus versus everolimus alone to determine safety and efficacy of the combination. Subjects will receive RX-0201 at the dose identified in Stage 1, in combination with everolimus or everolimus alone. Subjects will be randomized in a 1:2 ratio (i.e., up to 10 subjects in the everolimus alone arm and up to 20 subjects in the everolimus/RX-0201 arm).

Primary Objectives:
• To determine the maximum tolerated dose (MTD) of RX-0201, up to a target dose of 250 mg/m²/day, when given in combination with everolimus (Stage 1)
• To determine progression free survival in subjects with advanced renal cell carcinoma treated with the combination of RX-0201 and everolimus versus everolimus alone (Stage 2)

Secondary Objectives:
• To assess the pharmacokinetics of RX-0201 in combination with everolimus (Stage 1)
• To evaluate parameters of clinical benefit as measured by duration of response, time to response, and response rate (Stage 2)
• To evaluate the safety and tolerability of RX-0201 in combination with everolimus versus everolimus alone (Stage 1 and Stage 2)

Primary Endpoints:
• Incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities (Stage 1)
• Progression free survival (Stage 2)

Secondary Endpoints:
• Pharmacokinetic profile of RX-0201 (Stage 1)
• Incidence of adverse events, changes in clinical laboratory tests and vital signs over time (Stage 1 and Stage 2)
• Tumor response, duration of response, time to response, and response rates (Stage 2)

Preliminary Response Data

<table>
<thead>
<tr>
<th>Previous Therapies (Best Response)</th>
<th>RX-0201 Dose (mg/m²/day)</th>
<th>Days of Stable Disease</th>
<th>Response/Percent Reduction</th>
<th>Reason for Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib (PD)</td>
<td>125</td>
<td>334</td>
<td>SD/ 15% reduction (see image below)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Pazopanib (PD)</td>
<td>125</td>
<td>26</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Sunitinib (CR)</td>
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<td>SD/ 0% Consent Withdrawal</td>
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<tr>
<td>Pazopanib (PD)</td>
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<td>16</td>
<td>NE Unrelated AE</td>
<td></td>
</tr>
<tr>
<td>Sunitinib (NE)</td>
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<td>PD</td>
<td></td>
</tr>
<tr>
<td>Pazopanib (NE)</td>
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<td>PD</td>
<td></td>
</tr>
<tr>
<td>Pazopanib (PD)</td>
<td>200</td>
<td>18</td>
<td>N/A</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

AE = Adverse Event; CR = Complete Response; N/A = Not Applicable; NE = Not Evaluable; PD = Progressive Disease; SD = Stable Disease; U = Unknown

Conclusions
• At the dose levels tested, RX-0201, in combination with everolimus, appears to be safe and well tolerated and shows early signs of clinical activity.
• No dose limiting toxicities (DLTs) have been reported to date.
• In Stage 1 of this Phase 2a study, testing last dose level (250 mg/m²/day) is ongoing.