RX-0201, An Anti-Sense Targeting AKT-1 to Treat Metastatic Renal Cancer - Preliminary Stage 1 Data

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Abstract

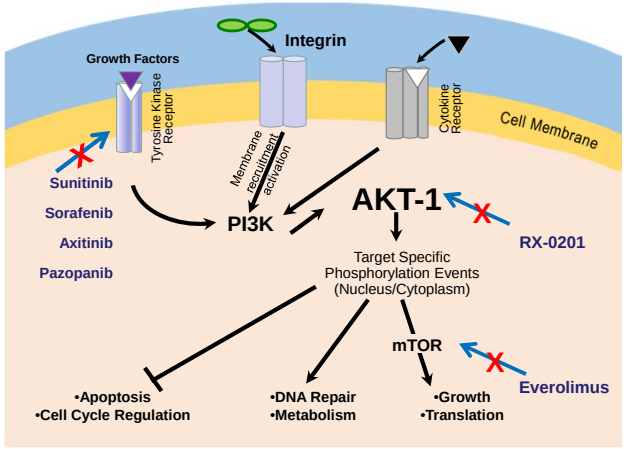
Background: RX-0201 is a 20-mer oligonucleotide that is complementary to AKT-1 messenger ribonucleic acid (mRNA). The specificity of RX-0201 mediated effect on AKT-1 mRNA levels was examined in human renal cell carcinoma (von Hippel-Lindau protein-deficient renal cell carcinoma cell line) UMRC2 cells 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/m^2/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/m^2/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/m^2/day (n = 3) and 200 mg/m^2/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.
NCT02089334

Proposed Mechanism



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 vs everolimus alone to treat subjects with advanced renal cell carcinoma

Stage 1 is an open-label, dose-escalation study designed to identify a safe and tolerable dose of Archexin® (RX-0201) when given in combination with everolimus

Stage 2 is the 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).

Treatment: RX-0201 is administered by continuous IV infusion for 14 days followed by 1 week of rest.

Dosing: The RX-0201 dose (125, 200 and 250 mg/m^2/day) will be escalated until the maximum tolerated dose or target dose is achieved. The dose of RX-0201 identified in Stage 1 will used in the dose expansion portion (Stage 2).

Current Dose: 250 mg/m^2/day

Study Objectives & Endpoints

Primary Objectives:

- To determine the maximum tolerated dose (MTD) of RX-0201, up to a target dose of 250 mg/m^2/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)

For further information about RX-0201 and Rexahn Pharmaceuticals
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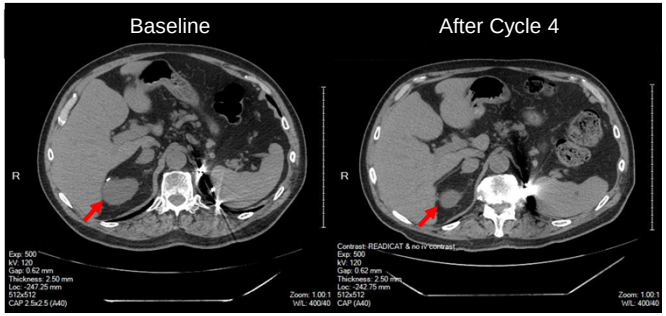
Preliminary Response Data

Previous Therapies (Best Response)	RX-0201 Dose (mg/m^2/day)	Days of Stable Disease	Response/ Percent Reduction	Reason for Discontinuation
Sunitinib (PD)	125	334	SD/ 15% reduction (see image below)	Ongoing
Pazopanib (PD) Axitinib (PD)	125	26	PD	PD
Sunitinib (CR)	125	170	SD/ 0%	Consent Withdrawal
Pazopanib (PD)	200	16	NE	Unrelated AE
Sunitinib (NE) Pazopanib (NE) Axitinib (PD)	200	51	PD	PD
Pazopanib (U)	200	42	PD	PD
Sunitinib (PD) Axitinib (PD)	200	18	N/A	Ongoing

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



Preliminary Adverse Event Profile

Most Frequent Adverse Events	Related to RX-0201 and everolimus	Related to everolimus only	Subject Total N = 7
Preferred Term			n
Thrombocytopenia	2*	2*	4
Feces discolored		2	2
Nausea		2	2
Neutropenia		2*	2
Rash	2		2

* At least one subject experienced an event graded as Severe

- Most events were reported as mild or moderate.

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/m^2/day) is ongoing.