Archexin, A Novel AKT-1 Specific Inhibitor for the Treatment of Metastatic Renal Cancer – Preliminary Stage 1 Data

Scott Tagawa[1], Gurkamal S. Chatta[2], Neeraj Agarwal[3] Reza Mazhari[4] and Ely Benaim[4],
[1]Weill Cornell Medical College/New York Presbyterian Hospital, [2]Virginia Mason Medical Center, [3]University of Utah Huntsman Cancer Institute, [4]Rexahn Pharmaceuticals, Inc.

Abstract #550

Background: Archexin® (RX-0201) is a 20-mer oligonucleotide that is complementary to AKT-1 messenger ribonucleic acid (mRNA). The specificity of Archexin mediated effect on AKT-1 mRNA levels, in human renal cell carcinoma (von Hippel-Lindau protein-deficient renal cell carcinoma cell line) UMRC2 cells results in a reduction of AKT-1 mRNA levels. In a single agent phase 1 study the maximum tolerated dose of Archexin was 250 mg/m2/day.

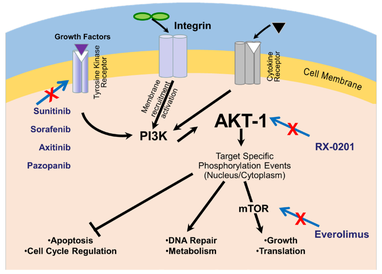
Methods: The current study is a proof of concept phase 1b/2, multicenter, open label study for subjects who have progressed on at least 1 VEGF-targeted therapy conducted in 2 stages. Stage 1 is an open-label, dose-escalation phase 1b study of Archexin administered in combination with everolimus. Archexin is administered by a 24 hour continuous intravenous infusion for 14 days followed by 7 days of rest. It is hypothesized that 250 mg/m^2/day or a lower dose of Archexin will be identified as safe and well-tolerated when administered in combination with 10 mg of everolimus. The dose of Archexin identified in Stage 1 will be studied further in Stage 2 which is the randomized, open-label, 2-arm study of Archexin in combination with 10 mg of everolimus versus 10 mg of everolimus alone. Plasma concentrations were measured using a validated LC MS/MS assay, and noncompartmental pharmacokinetic parameters were calculated using WinNonlin, Version 6.4.

Results: Five subjects with clear cell renal carcinoma received 125 mg/m^2/day (n=3) or 200 mg/m^2/day (n=2) of Archexin with 10 mg of everolimus administered daily. Two subjects have had stable disease for 160 and 257 days. The most frequently reported treatment related adverse events for the combination were thrombocytopenia, vomiting and fatigue; no dose limiting toxicities have been reported at this time. At all dose levels post-infusion, Archexin plasma concentrations increased rapidly and quickly reached a virtual plateau. Upon cessation of infusion on Day 14, plasma concentrations declined rapidly.

Conclusions: At the dose levels tested, Archexin, in combination with everolimus, appears to be well tolerated in patients with metastatic renal cancer. Dose escalation/modification is ongoing to determine the recommended phase 2 dose of Archexin to be studied further in Stage 2 (randomized) when combined with everolimus.

NCT02089334

Proposed Mechanism of Action



Stage 1 Study Design and Objectives

Methodology: This study is a 2-stage multi-center, open-label study to assess the safety and tolerability of 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 RX-0201 when given in combination with everolimus

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

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

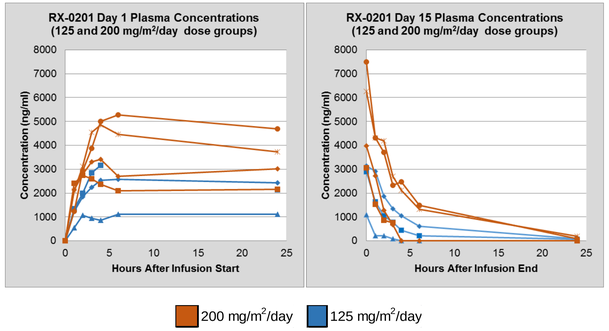
Secondary Objectives:

- To assess the pharmacokinetics of RX-0201 in combination with everolimus
- To evaluate the safety and tolerability of RX-0201 in combination with everolimus versus everolimus alone

Stage 1 Demographics

- 7 Males; 3 Females
- Median Age: 60 years; Range: 44-78 years
- Median Number of Prior Therapies: 1

Stage 1 Preliminary PK Data



PK Parameter	Day 1	
Dose	125 mg/m^2/day	200 mg/m^2/day
AUC last (ng•hr/ml)	43953 ± 19436	77638 ± 26512
Cmax (ng/ml)	2080 ± 1055	3936 ± 1190
Tmax (h)	6	4

PK Parameter	Day 15	
Dose	125 mg/m^2/day	200 mg/m^2/day
AUCinf (ng•hr/ml)	5180 ± 7280	14106 ± 13244
$T_{1/2}$ (h)	4 ± 3	3 ± 2
Cmax (ng/ml)	2153 ± 1116	4886 ± 2036
CL (L/h)	4.5 ± 2.8	3.5 ± 1.4

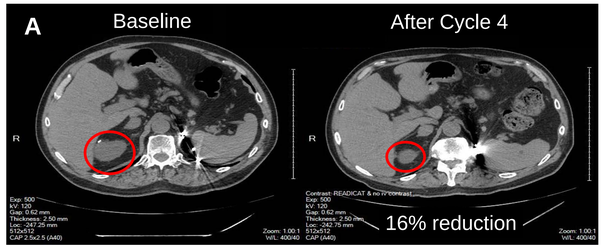
- RX-0201 exposure is dose proportional and appears to slightly accumulate during the dosing period. Upon cessation of the 14-day infusion, plasma concentrations decline rapidly with a mean $T_{1/2}$ of 3.98 hours (125 mg/m^2/day) and 2.65 hours (200 mg/m^2/day)

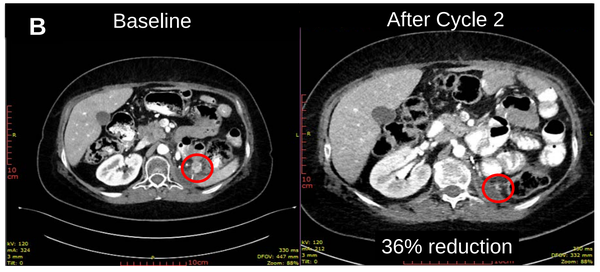
Stage 1 Response Data

- At the lowest dose level (125 mg/m^2/day) one subject has had stable disease for more than 1 year and experienced a 16% reduction in a right adrenal lesion after 4 cycles of treatment.
- At the second dose level (200 mg/m^2/day) one subject's hypervascular mass just anterior to the nephrectomy bed has decreased 36% in size after 2 cycles of treatment.
- Treatment at the target dose level (250 mg/m^2/day) is ongoing.

Previous Therapies (Best Response)	RX-0201 Dose (mg/m^2/day)	Days of Stable Disease	Response/ Percent Reduction	Reason for Discontinuation
Sunitinib (PD)	125	383	SD/ 16% reduction (see image set A)	Subject Withdrawal
Pazopanib (PD) Axitinib (PD)	125	26	PD	PD
Sunitinib (CR)	125	191	SD/ 0%	Subject Withdrawal
Pazopanib (PD)	200	16	NE	Unrelated AE
Sunitinib (NE) Pazopanib (NE) Axitinib (PD)	200	51	PD	PD
Pazopanib (U)	200	43	PD	PD
Sunitinib (PD) Axitinib (PD)	200	87	SD/ 36% reduction (see image set B)	Ongoing
Pazopanib (PR)	250	23	N/A	Unrelated AE
IL-2 (PR) Pazopanib (PR)	250	23	N/A	Ongoing
Sunitinib (PD)	250	9	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.
- No DLTs occurred at any dose level tested

Conclusions

- RX-0201 in combination with everolimus is safe and well-tolerated at doses up to 200 mg/m^2/day.
- Exposure of RX-0201 is dose proportional and declines rapidly upon cessation of infusion.
- At the dose levels tested, RX-0201, in combination with everolimus, shows early signs of clinical activity. Clinical activity will be further assessed in the randomized Stage 2 portion of the study.

For further information about RX-0201 and Rexahn Pharmaceuticals
please contact Dr. Ely Benaim: benaime@rexahn.com, (240) 268-5300 x 304