Phase Ib/II Study of RX-0201, a novel AKT-1 antisense, combined with everolimus to treat metastatic clear cell renal carcinoma – Phase Ib results

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Abstract # CT114

Background: RX-0201, a novel, oligonucleotide that binds native AKT-1 mRNA, prevents downstream phosphorylation to p-AKT. RX-0201, in combination with everolimus, additively inhibited Caki-1 cell growth in vitro and is in development for the treatment of metastatic clear cell renal carcinoma

Methods: The phase 1b/2 proof of concept, multicenter, open label study is conducted in 2 stages. The Phase 1b was a dose-escalation study of RX-0201 administered in combination with everolimus. RX-0201 was administered as a continuous intravenous infusion for 14 days followed by 7 days of rest; everolimus was administered at a starting dose of 10mg once daily. Subjects were enrolled at increasing doses of RX-0201 in a modified 3+3 design. Plasma concentrations were measured in Phase 1b and noncompartmental pharmacokinetic parameters were calculated using WinNonlin, Version 6.4. The dose of RX-0201 identified in Phase 1 is being studied further in Phase 2, which is the randomized, 2-arm study of RX-0201 in combination with everolimus versus everolimus alone.

Results: In the Phase 1b, seven males and three females, (median age 60 years) were treated with 125 mg/m^2/day (n=3), 200 mg/m^2/day (n=4), and 250 mg/m^2/day (n=3) RX-0201 in combination with 10 mg everolimus. They received 1-3 lines of therapy prior to study entry (median = 1). The most common toxicities attributed to the combination were rash, mouth ulceration, weight loss, thrombocytopenia, facial edema, fatigue, and pruritus. No significant events were attributed to RX-0201 alone. Most events (81%) were mild or moderate in severity. Based on the tolerability, 250 mg/m^2/day RX-0201 dose was declared the recommended phase 2 dose. Three subjects in the phase 1b have experienced stable disease for 383, 191, and 122 days; a tumor burden reduction of 16 and 36% was seen in 2 subjects. RX-0201 PK demonstrated a dose proportional exposure.

Conclusions: RX-0201, in combination with everolimus, appears to be safe and well tolerated in patients with metastatic renal cancer at doses up to 250 mg/m^2/day. A randomized Phase 2 clinical trial is currently ongoing.

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Study Design and Objectives

Methodology: The Phase 1b/2 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.

Phase 1b (Stage 1): was 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) were escalated until the maximum tolerated dose or target dose was achieved. The dose of RX-0201 identified in Phase 1 (250 mg/m^2/day) is being used in the randomized dose expansion portion (Phase 2/ Stage 2).

Phase 1b Primary Objective:

- 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

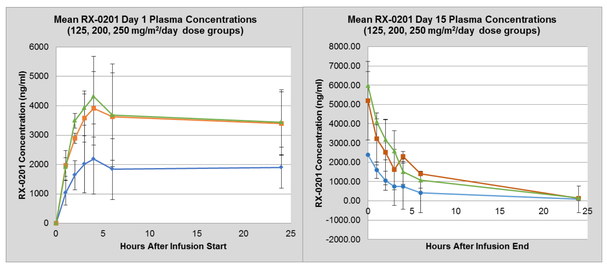
Phase 1b Secondary Objectives:

- 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

Demographics

- 7 Males; 3 Females
- Median Age: 60 years; Range: 44-78 years
- Median Number of Prior Therapies: 1
- Median ECOG Performance status at screening = 1; range 0-2

RX-0201 Pharmacokinetic Data



PK Parameter	Day 1		
Dose	125 mg/m^2/day	200 mg/m^2/day	250 mg/m^2/day
AUClast (ng·hr/ml)	43953 ± 19436	77638 ± 26512	71351 ± 30419
Cmax (ng/ml)	2080 ± 1055	3936 ± 1190	3757 ± 1254
Tmax (h)	6	4	4

PK Parameter	Day 15		
Dose	125 mg/m^2/day	200 mg/m^2/day	250 mg/m^2/day
AUCinf (ng·hr/ml)	5180 ± 7280	14106 ± 13244	21858 ± 3079
$T_{1/2}$ (h)	4 ± 3	3 ± 2	6 ± 0
Cmax (ng/ml)	2153 ± 1116	4886 ± 2036	5386 ± 1044
CL (L/h)	4.5 ± 2.8	3.5 ± 1.4	4.2 ± 0.9

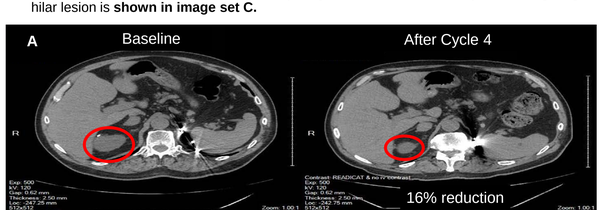
- RX-0201 exposure rapidly rises to steady state in Day 1 and accumulates slightly during the dosing period.
- Upon cessation of the 14-day infusion, plasma concentrations decline rapidly with a mean $T_{1/2}$ of 4.0 hours (125 mg/m^2/day), 2.7 hours (200 mg/m^2/day), and 6.0 hours (250 mg/m^2/day).
- Further testing of peak RX-0201 concentrations will occur in Stage 2.

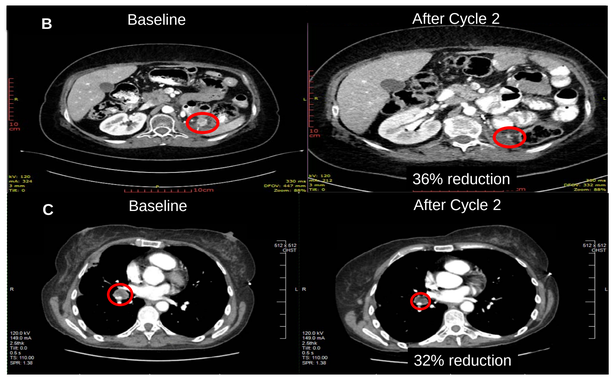
Response Data

Previous Therapies (Best Response)	RX-0201 Dose (mg/m^2/day)	Number of Cycles received	Days of Stable Disease	Best Response/ % Reduction	Reason for Discontinuation
Sunitinib (PD)	125/ 200	17	383	SD/ 16% reduction	Subject Withdrawal
Pazopanib (PD) Axitinib (PD)	125	1	26	PD	PD
Sunitinib (CR)	125	8	191	SD/ 0%	Subject Withdrawal
Pazopanib (PD)	200	<1	16	NE	Unrelated AE
Sunitinib (NE) Pazopanib (NE) Axitinib (PD)	200	<2	51	PD	PD
Pazopanib (U)	200	2	43	PD	PD
Sunitinib (PD) Axitinib (PD)	200/ 250	8	176	SD/ 36% reduction	PD
Pazopanib (PR)	250	1	23	N/A	Unrelated AE
IL-2 (PR) Pazopanib (PR)	250	<2	37	PD	PD
Sunitinib (PD)	250	6	106	SD/ 32% reduction	Ongoing

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

- Out of ten patients dosed to date, four have demonstrated stable disease for a median of 183.5 days, (range 106-383 days.)
- 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. **See image set A.**
- 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. **See image set B.**
- At the target dose level (250 mg/m^2/day) one subject experienced an unconfirmed 17% overall reduction in lesions (RECIST v 1.1) range 6% to 37.5% after 2 cycles. A single right hilar lesion is **shown in image set C.**





Safety Data

Most Frequent Adverse Events	Related to RX-0201 and everolimus	Related to everolimus only	Subject Total N = 10
Preferred Term			n (%)
Thrombocytopenia	2*	2*	4 (40%)
Nausea	1	3	4 (40%)
Rash	3	0	3 (30%)
Fatigue	2	0	2 (20%)
Anemia	1	1	2 (20%)
Diarrhea	1*	1	2 (20%)
Mouth ulceration	1	1	2 (20%)
Feces discolored	0	2	2 (20%)

* At least one subject experienced an event graded as Severe

- Most events (79%) were reported as mild or moderate. No dose limiting toxicities occurred.

Conclusions

- RX-0201 in combination with everolimus is safe and well-tolerated at doses up to 250 mg/m^2/day.
- Exposure of RX-0201 is dose proportional and declines rapidly upon cessation of infusion.
- RX-0201, in combination with everolimus, continues to show early signs of clinical activity. Clinical activity is being further assessed in the randomized Phase 2 portion of the study testing RX-0201 + everolimus vs everolimus alone.

For further information about RX-0201 and Rexahn Pharmaceuticals
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