Results from a Phase 1b/2 Study of RX-0201, a novel AKT-1 antisense, combined with everolimus to treat metastatic clear cell renal carcinoma

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Abstract #2559

RX-0201 is a novel, oligonucleotide that binds native AKT-1 mRNA, preventing downstream phosphorylation to p-AKT. RX-0201, in combination with everolimus, to treat metastatic clear cell renal carcinoma. In vitro RX-0201, in combination with everolimus, additively inhibited Caki-1 cell growth.

The Phase 1b/2 proof-of-concept, multicenter, open label study is conducted in 2 stages (NCT02089334). Stage 1 is a dose-escalation Phase 1b/2 study of RX-0201 in combination with everolimus (10 mg daily). RX-0201 was given as a continuous intravenous infusion for 14 days followed by 7 days of rest. Subjects were enrolled at increasing doses of RX-0201 in a 3+3 design. The target dose of RX-0201 identified in Stage 1 is being further evaluated in Stage 2, which is a randomized, 2-arm study of RX-0201 in combination with everolimus versus everolimus alone. Plasma concentrations were measured in Stage 1 and noncompartmental pharmacokinetic parameters were calculated using WinNonlin, Version 6.4.

In Stage 1 of the Phase 1b study, subjects 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. Seven males and three females, median age 61 years, were treated. Subjects received 1-3 treatments prior to study entry (median = 1). The most common toxicities attributed to the combination were rash, mouth ulceration, decreased weight, 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 Stage 2 dose. Four subjects in the Stage 1 of Phase 1b study have experienced stable disease for 383, 191, 129 and 58 days; also a tumor burden reduction from 16% to 38.5% was seen in four subjects. RX-0201 PK demonstrated a dose proportional exposure.

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. Stage 2 of the Phase 1b/2 clinical study is currently ongoing.

Study Design and Objectives

Methodology: The Phase 1b/2 study is a 2-stage, multicenter, 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

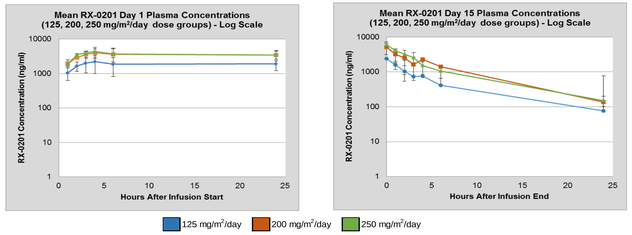
Phase 1b Secondary Objectives:

- 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 and Prior Therapies

Parameter	Overall
Gender, n (%)	10
Female	3 (30%)
Male	7 (70%)
Median age (range)	60 years (44 – 78 years)
Race, n (%)	
White	6 (60%)
American Indian or Alaska Native	1 (10%)
Black or African American	1 (10%)
Native Hawaiian or Other Pacific Islander	1 (10%)
Other	1 (10%)
Median ECOG performance status at screening, (range)	1 (0 - 2)
Median ECOG performance status on study, (range)	0 (0 - 2)
Median number of prior anticancer treatments (range)	1 (1 – 3)

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

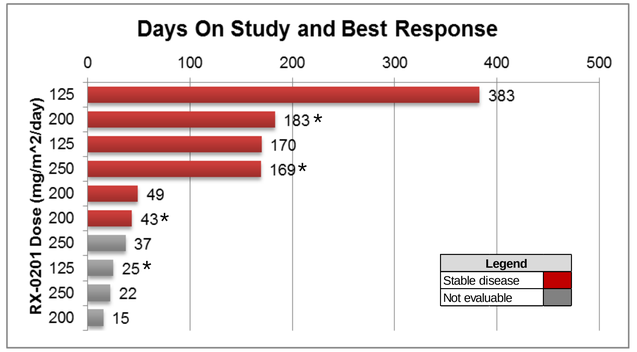
- RX-0201 exposure rapidly rose to steady state in Day 1 and accumulated slightly during the dosing period.
- Upon cessation of the 14-day infusion, plasma concentrations declined rapidly with a mean $T_{1/2}$ of 4.0 hours (125 mg/m^2/day), 2.7 hours (200 mg/m^2/day), and 6.0 hours (250 mg/m^2/day).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

Safety Data

Most Common Treatment-Related Treatment Emergent Adverse Events by Severity (>10% of subjects) (Safety)

Treatment Emergent Adverse Event	Number of Subjects (N=10)				Total n (%)
	Grade 1	Grade 2	Grade 3	Grade 4	
Stomatitis	4	0	2	0	6 (60%)
Thrombocytopenia	0	1	3	1	5 (50%)
Nausea	4	0	0	0	4 (40%)
Anemia	1	2	0	0	3 (30%)
Vomiting	3	0	0	0	3 (40%)
Diarrhea	1	0	1	0	2 (20%)
Fatigue	1	1	0	0	2 (20%)
Contusion	2	0	0	0	2 (20%)
Dysgeusia	2	0	0	0	2 (20%)
Feces discolored	2	0	0	0	2 (20%)
Neutropenia	0	1	0	1	2 (20%)
Pruritus	2	0	0	0	2 (20%)

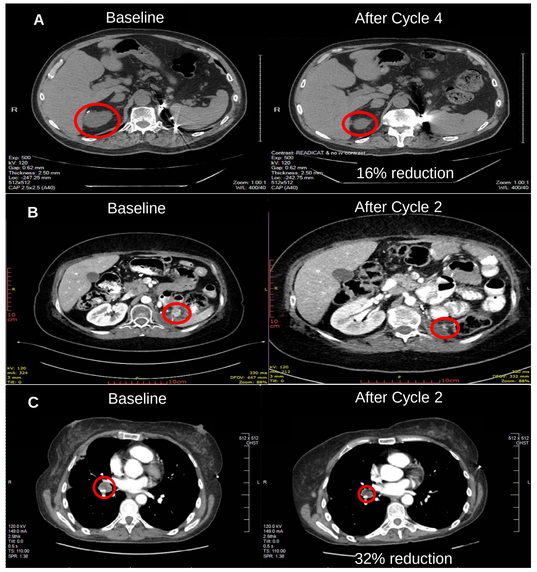
Response Data



* Discontinuation due to progressive disease

- Out of 10 patients dosed in Phase 1b (Stage 1), 6 demonstrated stable disease for a median of 165.5 days, (range 43-383 days).

- At the lowest dose level (125 mg/m^2/day) one subject experienced stable disease for more than 1 year and 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 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.**



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.

Investigator Disclosures

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