

Results of a Phase 2 Study to Evaluate the Safety and Efficacy of RX-0201 in Combination with Everolimus in Subjects with Metastatic Renal Cell Carcinoma (mRCC)

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Abstract #646

Background: RX-0201 is a novel 20-mer oligonucleotide that binds to mRNA coding for AKT-1, preventing AKT-1 expression and limiting the amount of downstream p-AKT. In vitro RX-0201, in combination with everolimus, additively inhibited Caki-1 cell growth. RX-0201, in combination with everolimus, to treat mRCC was evaluated in a Phase 1b/2 clinical study.

Methods: This Phase 1b/2 study (2-stage design, [NCT02089334](#)) evaluated the efficacy and safety of RX-0201 in combination with everolimus in eligible subjects with mRCC. Eligible subjects must have had confirmed histologic or cytologic evidence of renal cancer with a clear cell component, measurable disease as defined by RECIST v1.1, received at least 1 course of therapy with a VEGFR inhibitor and progressed within 6 months of planned first dose of on study treatment. In Phase 1 subjects were enrolled at increasing doses of RX-0201 (delivered via continuous IV for 14 days) in combination with 10 mg/day everolimus in a modified 3+3 design. The target dose of RX-0201 identified in Phase 1, 250 mg/m²/day, was further evaluated in Phase 2. Primary objectives included the safety and efficacy at the recommended Phase 2 dose. The Phase 2 primary endpoint was progression free survival (PFS) benefit for at least 4.5 months.

Results: Eleven subjects (7 males, 4 females) with mRCC were treated with RX-0201 (250 mg/m²/day) + everolimus (10 mg/ day) in Phase 2. The median age was 64 years, ECOG performance status at screening was 0 to 1, and 55% received ≥ 3 prior therapies. The median PFS in evaluable subjects was 4.9 months. Four subjects had stable disease after 6 months of treatment. The most frequent related adverse events (>15%) were G1/2 epistaxis, G3 fatigue, G1/2 nausea and G1 vomiting.

Conclusions: In this mRCC population with extensive prior therapy, RX-0201 in combination with everolimus was safe, well-tolerated, and showed promising efficacy. The results also support the therapeutic significance of the AKT-1/mTOR pathway in mRCC.

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 2 Design: an open-label, phase 2 study of RX-0201 in combination with everolimus

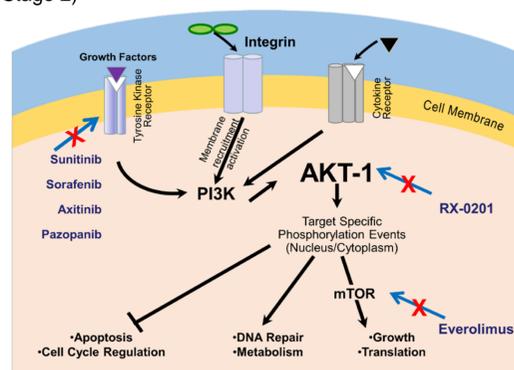
Treatment: RX-0201 (250 mg/m²/day) is administered by continuous IV infusion for 14 days followed by 1 week of rest. Everolimus (10 mg) was administered orally once daily. The dose was determined in the Phase 1 portion of the study (Agarwal N, et al., Journal of Clinical Oncology 34, no. 15_suppl (May 2016) 2559-2559).

Phase 2 Primary Objective:

- To determine progression free survival in subjects with advanced renal cell carcinoma treated with the combination of RX-0201 and everolimus versus everolimus alone

Phase 2 Secondary Objectives:

- 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)



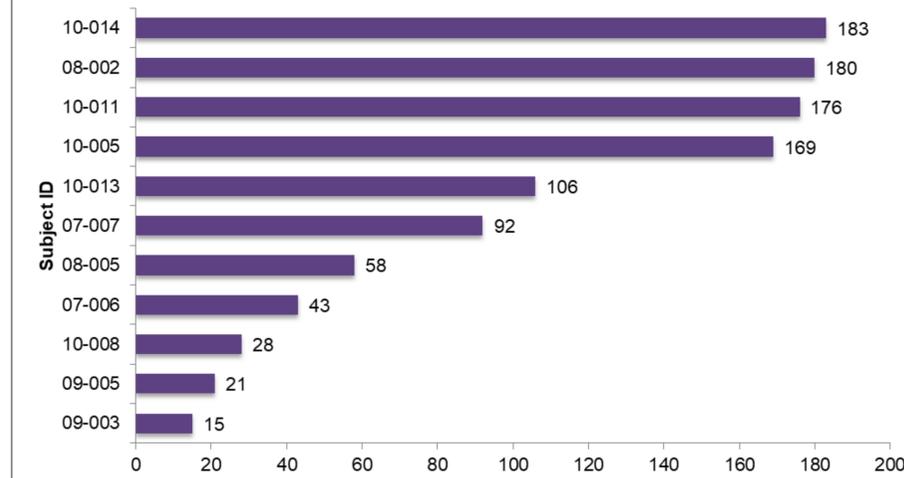
Baseline Characteristics (N=11)

Age (No. of yr.)	Sex — no. (%)
Median	64
Range	53-72
	Male
	Female
	7 (64)
	4 (36)
Race and Ethnic Group — no. (%)	ECOG score — no. (%)
Black or African American	1 (9)
American Indian or Alaska Native	1 (9)
Asian	1 (9)
White	8 (72)
Hispanic	1 (9)
Non-Hispanic	10 (91)
	ECOG = 0
	ECOG = 1
	6 (55)
	5 (45)
	Prior Therapies — no. (%)
	1
	2
	≥3
	1
	4
	6

Results

- Recruitment for this study was significantly affected by a change in the standard of care for advanced RCC due to the approval of 3 new therapies (nivolumab, cabozantinib, and lenvatinib + everolimus). Therefore enrollment in the everolimus alone arm was stopped early in the study due to a change in the standard of care and slow accrual.
- Eleven subjects were enrolled and treated with 250 mg/m²/day IV RX-0201 14-day in combination with 10 mg everolimus. 8 subjects were response evaluable with at least 1 on-study scan
- The median progression free survival (PFS) in Phase 2 evaluable subjects was 4.9 months. The median PFS (Analysis Dataset) was 110 days (3.7 months)
- Most Treatment Emergent Adverse Events (TEAEs) related to the combination were Grade 1 - 2 (68%). The most common related Grade 3/4 TEAE was fatigue (2/ 18%).

Progression Free Survival (Phase 2) - Censored



Safety

TEAE	Grade 1/2	Grade 3/4	Total
Epistaxis	2 (18.1)	0 (0)	2 (18.1)
Fatigue	0 (0)	2 (18.1)	2 (18.1)
Nausea	2 (18.1)	0 (0)	2 (18.1)
Vomiting	2 (18.1)	0 (0)	2 (18.1)
Anaemia	1 (9)	0 (0)	1 (9)
Contusion	1 (9)	0 (0)	1 (9)
Decreased appetite	1 (9)	0 (0)	1 (9)
Excoriation	1 (9)	0 (0)	1 (9)
Haematuria	1 (9)	0 (0)	1 (9)
Hypophosphataemia	0 (0)	1 (9)	1 (9)
Leukopenia	0 (0)	1 (9)	1 (9)
Neutropenia	0 (0)	1 (9)	1 (9)
Pyrexia	1 (9)	0 (0)	1 (9)
Stomatitis	1 (9)	0 (0)	1 (9)
Thrombocytopenia	0 (0)	1 (9)	1 (9)

Pharmacokinetics

PK Parameter	RX-0201 Dose (mg/ m ² / day)		
	125	200	250
C _{ss} (ng/mL)	1,626 [73.5] (2)	3,283 [.] (1)	5,147 [.] (1)
λ _z (/hr)	—†	0.6348 [.] (1)	—†
t _{1/2} (hr)	—†	1.09 [.] (1)	—†
CL (mL/hr)	93,090 [50.9] (2)	73,731 [.] (1)	56,797 [.] (1)
(mL/hr/kg)	990 [57.2] (2)	998 [.] (1)	0,699 [.] (1)
V _z (L)	—†	116 [.] (1)	—†
(L/kg)	—†	1.57 [.] (1)	—†

*Geometric mean [geometric %CV] (N). †Parameter could not be estimated for any subject in this dose group.

Conclusions

- Due to the low numbers of subjects treated it was not possible to adequately evaluate an efficacy or safety benefit of RX-0201, when combined with everolimus as a salvage treatment of subjects with advanced RCC.
 - Historical progression free survival of everolimus alone is 4.0 months
 - The median progression free survival of this study was 4.9 when the data were censored.
- RX-0201 + everolimus appears to be safe and tolerable
- The PK of RX-0201 does not appear to be altered when combined with everolimus