STATISTICAL ANALYSIS PLAN

Study Title:	**A Multi-Center, Open-label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of RX-0201 in Combination With Everolimus to Treat Subjects With Advanced Renal Cell Carcinoma** (NCT02089334)
Sponsor	Rexahn Pharmaceuticals, Inc 15245 Shady Grove Road, Suite 455 Rockville, MD 20850 USA Telephone (240) 268-5300 Fax (240) 268-5310
Name of Test Drug:	RX-0201
Protocol:	RX-0201-P2-A-09
Phase:	Phase 1b/2
Analysis Plan Version	Version 1.0
Analysis Plan Date	29 May, 2018
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Version	Version Data	Reasons for Modification
0.1	**August 8, 2015**	**Issued by Cliff Meng based on Protocol Amendment #2**
0.2	**May 29, 2018**	**JC Kuan modified the SAP based on Protocol Amendment #4**
0.3	**October 08, 2018**	**JC Kuan modified the SAP based on the telecon with Rexahn on Sep 12, 2018.**

1 Table of Contents

2 Abbreviations and Definitions

AE	Adverse Event
CR	Complete Response (RECIST criteria)
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ITT	Intent to Treat
MTD	Maximum Tolerated Dose
NE	Not evaluable (RECIST criteria)
PD	Progressive Disease (RECIST criteria)
PFS	Progression-Free Survival
PR	Partial Response (RECIST criteria)
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	Stable Disease (RECIST criteria)
SOC	System Organ Class
WHO Drug	Word Health Organization Drug Dictionary Enhanced

3 Introduction

3.1 Preface

This document describes the data analysis specifications for Rexahn Pharmaceuticals protocol RX-0201-P2-A-09 titled: "A Multicenter, Open-label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of RX-0201 in Combination With Everolimus to Treat Subjects With Advanced Renal Cell Carcinoma". This version of the statistical analysis plan dated April 3, 2018 was prepared in accordance with the protocol RX-0201-P2-A-09 Amendment 04 dated March 8, 2017. Other related documents are the electronic case report form (eCRF) data definition fields and data set definitions.

3.2 Purpose of the Analyses

The purpose of this Statistical Analysis Plan (SAP) is to provide a framework in which answers to the protocol objectives may be achieved in a statistically rigorous fashion using methods identified prior to database lock. Any deviations from these methods must be documented in the final clinical study report.

4 Study Objectives and Endpoints

4.1 Study Objectives

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 (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 objective(s):

- To assess the pharmacokinetics of RX-0201 in combination with everolimus (Stage 1)
- To evaluate parameters of clinical benefit of RX-0201 in combination with everolimus versus everolimus alone 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)

Exploratory objective:

- To investigate the effects of RX-0201 and everolimus on AKT pathway biomarkers, tumor apoptosis biomarkers and other biomarkers in blood or tumor samples (Stage 1 and Stage 2)
- To further evaluate the peak plasma concentration of RX-0201 at the target dose (Stage 2)

4.2 Endpoints

Primary Endpoint:

- The incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities (Stage 1)
- Progression-free survival at 4.5 months (Stage2)

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 rate, duration of response, time to response and response rates (Stage 2)

Exploratory Endpoint:

- Blood levels of AKT pathway biomarkers, tumor apoptosis biomarkers or other biomarkers (Stage 1 and Stage 2)
- Plasma concentration of RX-0201 at the end of infusion (Stage 2)

4.3 Derived variables

Subject Age

The subject's age will be calculated as the number of years from the subject's date of birth to his/her screening date: Age = ([Screening Date - Date of Birth] / 365.25).

Baseline

The baseline value for any variable will be the value measured before first administration of study-specified treatment. For variables/assessments not scheduled to be performed on study day 1 or that are missing at baseline, the baseline value will be the value from the screening period measured closest to study day 1.

Time from First Histopathological /Cytological Diagnosis to Screening Visit

Date of the first histopathological/cytological diagnosis will be captured in the EDC dataset. Date of screening visit will be captured in the Visit Date SAS dataset.

Dose-Limiting Toxicity (DLT)

The definition of DLT is described in Section 6.5of this SAP. Dose-limiting toxicity will be evaluated during Cycle 1 of treatment.For purposes of displaying DLTs on a per-subject and per-cohort basis,

the Electronic Data Capture (EDC) system will capture and identify whether or not a subject experiences a DLT in the AE dataset.

Maximum Tolerated Dose (MTD)

The determination of Maximum Tolerated Dose (MTD) is described in Section 6.4 of this SAP.

Response Evaluation Criteria in Solid Tumors (RECIST) Criteria: Version 1.1

RECIST v1.1 criteria are outlined in Appendix E of the protocol.

Overall Response Rate (ORR, Investigator Assessment)

The tables below provide time point overall responses for all possible combinations of tumor responses in subjects with target and non-target lesions, with or without new lesions, per RECIST v1.1.

A summary of the overall response status calculation at each time point is presented in Table 1 for subjects who have measurable lesions at baseline, and in Table 2 for subjects who have only non-measurable (therefore non-target) lesions at baseline. For data display and analysis purposes, the "BEST" overall response for each subject from all post-baseline time point overall responses will be used. The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence, or occurrence of intolerable toxicity, whatever comes first, taking, for target lesions, as reference for progressive disease, the smallest sum of diameters of target lesions recorded since the treatment started.

When no imaging/measurement is done at all at a particular time point, the subject will not be evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. Overall Response Rate (ORR) will be defined as the proportion of subjects with a best overall response of Complete Response (CR), Partial Response (PR), or Stable Disease (SD).

Table 1 Time point response for subjects with target (+/- non-target) lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR / Non-PD	No	PR

CR	NE	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable

Table 2 Time point response for subjects with non-target disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR / Non-PD	No	Non-CR / Non-PD (1)
Not all evaluated	No	NE
PD	Yes or No	PD
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

(1) Non-CR / non-PD is preferred over 'Stable Disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials. To assign this category when no lesions can be measured is not advised.

Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed not less than 4 weeks after the initial criteria for response are first met. In the case of SD, measurements must have met the SD criteria at least once

after study entry at a minimum interval (in general not less than 6 – 8 weeks) that is defined in the study protocol. Best overall response thus can be interpreted as shown in the Table below (Eisenhauer et al, 2009).

Table 3 Best overall response when confirmation of CR and PR required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	BEST overall response
CR	CR	CR
CR	PR	SD, PD, OR PR
CR	SD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD
PR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
NE	NE	NE

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

Appendix E of the protocol provides details on methods of measurements, documentation and evaluation of target / non-target lesions.

Time to Response

The Time to Response will be the time between initiation of treatment and first documentation of PR or CR.

Duration of Response

The duration of response will be the time from first documented response (CR or PR) until the earlier of either first documented tumor progression (PD) or death from any cause. Subjects achieving a CR or PR, who are alive without progression, are lost to follow up, or who have died without report of

progression as of the time of analysis will be censored at the date of last response assessment or last date on study, whichever is earliest.

Progression-Free Survival (PFS)

Progression-free survival will be defined as the time from date of initiation of treatment until the earlier of either first documented tumor progression (PD) or death from any cause. Subjects alive without progression or lost to follow-up at the time of analysis will be censored at the date of last response assessment. Progression free survival will be analyzed at 4.5 months (Stage 2).

5 Study Methods

5.1 General Study Design and Plan

This is a 2-stage phase 1b/2, multi-center, open-label study to assess the safety and tolerability of RX-0201 in combination with everolimus versus everolimus alone to treat subjects with advanced renal cell carcinoma. Approximately 32 subjects will be recruited and enrolled into the study over 20 centers in the US.

Stage 1 is an open-label, dose-escalation phase 1b study of RX-0201 to identify a safe and tolerable dose of RX-0201 up to a target dose of 250 mg/m^2/day when given in combination with everolimus. Approximately 9 subjects will be enrolled to receive the combination of everolimus and RX-0201 at increasing doses of RX-0201 to the MTD or up to a target dose of 250 mg/m^2/day. The number of subjects enrolled into Stage 1 will vary depending upon the number of dose levels needed to determine the MTD, up to a target dose of 250 mg/m^2/day.

Stage 2 is an open-label, 2-arm phase 2 study of RX-0201 in combination with everolimus versus everolimus alone. Approximately 3 additional subjects will be treated with everolimus alone arm and up to 20 subjects in the everolimus/RX-0201 arm.

Everolimus will be administered daily at 10 mg orally at approximately the same time each day consistently with or without food per the approved label instructions in Stage 1 and Stage 2.

RX-0201 will be administered at a starting dose of 125 mg/m^2/day, by a 24 hour continuous intravenous infusion for 14 days followed by 7 days of rest in each 21 day cycle. RX-0201 doses in Stage 1 will be escalated until a maximum tolerated dose (MTD) or a target dose of 250 mg/m^2/day is reached. The MTD or the target dose will be tested further in Stage 2.

For subjects assigned to receive RX-0201 and everolimus, a cycle will be defined as the period elapsing from the first day of RX-0201 administration through Day 21 of the cycle or to the recovery

from any adverse events sufficient that a new cycle of therapy can be administered (e.g., on Day 29 or Day 36), whichever occurs later. Once a new cycle starts, the prior cycle is considered to be completed. For subjects assigned to the everolimus only arm, a cycle will be defined as the period elapsing from the first day of everolimus administration through Day 21 of the cycle or to the recovery from any adverse events sufficient that a new cycle of therapy can be administered, whichever occurs laterSubjects in Stage 1 and Stage 2 may receive up to 8 cycles of combined therapy until withdrawal of consent, pregnancy, substantial noncompliance with study procedures, intolerable adverse event, documented radiological disease progression or death, principal investigator judgment that it is in the best interest of the subject to stop treatment, or study discontinuation. Subjects, who the principal investigator feels are receiving benefit, may continue to receive additional cycles of therapy following discussions with the Sponsor. Subjects randomized to the everolimus only treatment arm will complete the study after 8 cycles but may continue to receive everolimus off-study.

Each subject should complete all study procedures in approximately 8 months (i.e., screening period up to 14 days; treatment period up to eight 21-day cycles, safety follow-up approximately 30 days after the last dose of study medication). However, for subjects approved to receive additional treatment cycles, the duration may be longer than 8 months. The study duration is estimated at approximately 30 months.

5.2 Equivalence or Non-Inferiority Studies

No equivalence or non-inferiority test will be conducted in the analysis.

5.3 Inclusion-Exclusion Criteria and General Study Population Defined

5.3.1 Inclusion Criteria

Disease Related

- Documented histological or cytological diagnosis of renal cell cancer with a clear-cell component
- Measurable or evaluable disease defined by Response Evaluation Criteria for Solid Tumors (RECIST) ver. 1.1
- Must have received at least one course of therapy with a VEGFR-targeting tyrosine kinase inhibitor (eg, sorafenib, sunitinib, axitinib, pazopanib or tivozanib) and progressed within 6 months of planned first dose of study treatment.
- Prior therapy with cytokines (i.e., IL-2, Interferon) and/or VEGF-ligand inhibitors (i.e., bevacizumab) are permitted
- Prior vaccine therapy in the adjuvant setting is permitted
- Tissue blocks or tissue sections from initial diagnosis or upon diagnosis of advanced metastatic disease will be available for submission to the central laboratory within

approximately 4 weeks after initiation of study treatment; exceptions (e.g., histology determined by fine needle aspirate or tissue is no longer available) require written documentation of why a sample is not available and prior approval by the sponsor before enrollment/ randomization
- ECOG performance status of 0, 1 or 2
- Life expectancy > 3 months

Demographic

- Males and females ≥ 18 years of age at screening

Ethical

- Before any study-specific procedures are performed, written informed consent must be obtained

5.3.2 Exclusion Criteria

Disease Related

- Disease-associated symptoms requiring immediate therapy or other interventions
- Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 3 months before planned first dose of study drug

Laboratory

- Absolute neutrophil count < 1.5 x 10^9/L
- Platelet count < 100 x 10^9/L
- Hemoglobin < 9 g/dL
- Bilirubin > 1.5 X upper limit of normal (ULN)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 X ULN (OR > 5 X ULN in the presence of known liver metastases)
- Serum creatinine > 1.5 X ULN OR estimated creatinine clearance ≤ 60 ml/min (Cockroft-Gault)
- Partial thromboplastin time (PTT) > 1.25 X ULN
- Prothrombin time (PT) > 1.25 X ULN OR international normalization ratio (INR) > 1.4

Medications

- Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before planned first dose of study drug. Systemic treatment with radionuclides within 6 weeks before planned first dose of study drug. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible
- Prior treatment with everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor (e.g., temsirolimus)
- Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before planned first dose of study drug
- Receipt of any type of anticancer antibody (including investigational antibody) within 4 weeks before planned first dose of study drug
- Taking strong inducers or inhibitors of CYP450s for subjects receiving everolimus
- Chronic treatment with corticosteroids or other immunosuppressive agents
- Concomitant anticoagulation at therapeutic doses with oral anticoagulants or platelet

inhibitors
- Subjects with a known hypersensitivity to everolimus or other rapamycins (sirolimus, temsirolimus) or to its excipients
- Not recovered from toxicities related to any prior treatments, unless adverse events are clinically non-significant and/or stable on supportive therapy

General

- History of any medical, psychiatric, or social (e.g., addictive disorder) conditions, or laboratory abnormality that in the opinion of the investigator, may increase the risks associated with study participation or treatments that may interfere with the conduct of the study or the interpretation of study results
- Major surgery within 2 months before planned first dose of study drug. Complete wound healing from major surgery must have occurred within 1 month before planned first dose of study drug and from minor surgery at least 10 days before planned first dose of study drug
- Myocardial infarction within the previous 6 months before planned first dose of study drug
- Active infection requiring parenteral antibiotics within 2 weeks before planned first dose of study drug
- Diagnosis of another malignancy within 2 years before planned first dose of study drug, except for superficial skin cancers, or localized, low grade tumors;
- Currently enrolled in and has not yet completed at least 30 days since ending other investigational device or drug study before planned first dose of study drug, or subject is currently receiving other investigational agent(s).
- Prior or current history of hepatitis B, hepatitis C or human immunodeficiency virus
- Pregnant, planning a pregnancy or breastfeeding during the study
- Sexually active fertile subjects (male and female), must agree to use medically accepted methods of contraception during the course of the study and for 30 days after the last dose of study treatment. Female subjects must meet at least one of the following criteria:

    - be surgically sterile (i.e., have had bilateral tubal ligation, hysterectomy, or bilateral
    - oophorectomy at least 6 months before enrollment; appropriate documentation will be
    - required),
    - be post-menopausal for at least 12 months OR
    - if sexually active, be willing to use double-barrier contraception (e.g., condom with
    - spermicide), intrauterine device, steroidal contraceptive (oral, transdermal, implanted, or
    - injected) or other method, approved by the sponsor.
- Unwilling or unable to comply with study requirements or not available for follow-up assessments
- Any other major illnesses that in the investigator's judgment substantially increases the risk associated with the subject's participation in the study

5.4 Subject Enrollment/ Randomization and Blinding/ Subject Replacement

Subjects in Stage 1 will be enrolled to receive the combination everolimus with escalating doses of RX-0201. Subjects in Stage 2 will no longer be randomized to 1 of 2 treatment arms (i.e., everolimus versus everolimus/RX-0201). All subjects in Stage 2will now be assigned to the everolimus/ RX-0201 treatment arm. Subjects in Stage 1 who are enrolled but not treated and subjects who discontinue treatment before completion of Cycle 1 for reasons other than the occurrence of a DLT may be

replaced. Any replacement subject will be enrolled into the same dosing cohort as that for the subject who withdrew.

Subjects in Stage 2 who are enrolled but not treated will be replaced.

5.5 Study Variables

5.5.1 Definition of Dose-Limiting Toxicity

Reference should be made to the CTCAE, Version 4.03 for grading of the severity of adverse events and laboratory abnormalities. Dose-limiting toxicities (DLT) will be evaluated during Cycle 1 of treatment. These DLTs will be graded and documented according the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) (v4.03)A DLT will be defined as the occurrence of any of the following that are determined by the investigator to be related to RX-0201:

- Grade 4 neutropenia (ANC < 0.5 x 10^9/L) with fever or lasting 3 days or longer
- Any Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with ≥ Grade 1 hemorrhage
- Any ≥ Grade 3 coagulation abnormality (defined by PT and/or INR and PTT values) associated with clinical hemorrhage ≥ Grade 1.
- Nausea/vomiting ≥ Grade 3 despite maximal antiemetic therapy; diarrhea ≥ Grade 3 despite maximal anti-diarrheal therapy.
- Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)
- Any other non-hematological toxicity ≥ Grade 3 with the exception of alopecia

5.5.2 Dose Escalation and Definition of Maximum Tolerated Dose

Initially 3 subjects will be enrolled to receive everolimus plus 125 mg/m^2/day of RX-0201. Depending on whether there are any dose limiting toxicities (DLTs) attributed to RX-0201, the following dose-escalation decisions and rules will be followed:

Dose-escalation decisions:

Dose Group	Theoretical dose (mg/m2/da)	Escalation
1	125	-
2	200	1.60
3	250	1.25

Dose-escalation rules:

- If 0 of the first 3 subjects experience DLT during the first 3 weeks of treatment, then the dose will be escalated to the next higher level in 3 subsequent subjects.
- If 1 of the first 3 subjects experiences DLT at the current dose during the first 3 weeks of treatment, then 3 more subjects will be accrued at the same dose level.
- If 0 of the 3 additional subjects experience DLT during the first 3 weeks of treatment, then the dose will be escalated to the next higher level in 3 subsequent subjects.
- If ≥1 of the 3 additional subjects in a cohort experiences DLT in the first 3 weeks of treatment, the MTD has been exceeded and 3 more subjects will be treated at the next lower dose level (if only 3 subjects were previously treated at that prior dose level).
- If ≥2 of 3 or ≥2 of 6 subjects experience DLT during the first 3 weeks of treatment, then the MTD has been exceeded and 3 more subjects will be treated at the next lower dose level (if only 3 subjects were previously treated at that prior dose level).
- Each group of 3 subjects within a cohort must be observed for a minimum period of 3 weeks without DLT before subsequent subjects are enrolled at the next higher dose level.
- Escalation to the next dose level of the study can occur upon review of the safety data from all ongoing and previous subjects and with the concurrence of the study sponsor and the principal investigators.

In the event that attribution of causality of potential DLTs to study agent may be equivocal, discussions with the safety review committee will occur and additional subjects may be enrolled at that dose level. The decision to escalate to the next dose level will be based upon observation of DLTs during Cycle 1 from at least 3 subjects in the previous dose level. Reviews will be conducted by the safety review committee to monitor safety data on an ongoing basis throughout the study. In addition, the investigators and/or the Medical Monitor may prompt a meeting by the safety review committee at any time. Rexahn or its designee will notify the sites when enrollment into a dose level is complete and when the next dose level is open to enrollment during Stage 1.

5.5.3 Determination of MTD or the RX-0201 Recommended Stage 2 Starting Dose

The establishment of the MTD or the safety of the target RX-0201 dose of 250 mg/m^2/day will be based on a review of the overall safety data by the safety review committee. The MTD is the highest starting dose level associated with first-cycle DLTs in < 33.3% of subjects. Once the safety of the MTD of the target RX-0201 dose of 250 mg/m^2/day is initially established, additional subjects (up to 20 subjects total) will be enrolled to receive the target RX-0201 dose of 250 mg/m^2/day in Stage 2. Selection of a recommended Stage 2 starting dose from within the tested dose ranges and schedules will be based on evaluation of available safety information with findings regarding compliance, and achievement of targeted pharmacokinetic values.

6 Sample Size

Sample size calculation for this study has been empirically set. Approximately 32 subjects will be recruited and enrolled into the study over 20 centers in the US.

For Stage 1, approximately 9 subjects will be enrolled in to receive the combination of everolimus (10 mg) and RX-0201 at increasing doses of RX-0201 to the MTD or up to a target dose of 250 mg/m^2/day. For Stage 2, approximately 3 additional subjects will be treated with everolimus alone arm and up to 20 subjects in the everolimus/RX-0201.

7 General Considerations

The software used for all summary statistics and statistical analyses will be SAS Version 9.4 or later.

Safety, Efficacy, and PK assessments will be summarized separately for Stage 1 and Stage 2. Additional summaries and analyses of pooled Phase 1 and 2 data may also be generated based on applicability of dosing regimens.

Unless otherwise noted, data will be summarized in tabular format by increasing dose level of RX-0201 for the combination of RX-0201 and Everolimus in Stage 1, by combination of RX-0201 and Everolimus in Stage 2, and by RX-0201 dose level for the combination of RX-0201 and Everolimus Stage 2. All groups combined (i.e., Total/Overall column) will also be presented when appropriate. All study data documented on the eCRFs will be included in the study data listings.

7.1 Timing of Analyses

Analysis window is not defined in this study.

7.2 Analysis Population

7.2.1 Full Analysis Set

The Full Analysis set includes all enrolled subjects with subjects analyzed according to the treatment assigned at enrollment/randomization. All efficacy endpoints will be analyzed using the Full Analysis set.

7.2.2 Per Protocol Analysis Set

The Per-Protocol Analysis set includes all subjects without pre-specified major protocol deviations. Sensitivity analyses of some efficacy endpoints may be performed using the per-protocol analysis set.

7.2.3 Safety Analysis Set

The safety analysis set includes all subjects who receive at least one dose of study drug(s) with subjects analyzed according to the treatment received. All safety data will be analyzed in accordance with this analysis set. The safety analysis set will be defined as all subjects who receive at least 1 dose of study drug. These subjects will be analyzed according to the treatment received. All safety data will be analyzed in the safety analysis set.

7.2.4 Dose Limiting Toxicity Analysis Set

The dose limiting toxicity assessment set will include all evaluable subjects. An evaluable subject is any subject who experiences a dose limiting toxicity in the first 21 days of treatment or completes 2 weeks of RX-0201 treatment in cycle 1.

7.2.5 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set will include all enrolled subjects who undergo blood sampling during the study and have measurable concentrations of RX-0201 above the respective assays' limit of quantification at any time point after dosing.Evaluable for Tumor Response Analysis Set (Stage 2 only)

The analysis of objective response includes all subjects in the Full Analysis Set (and per-protocol set if applicable) with a uni-dimensional measurable lesion at baseline (as per RECIST 1.1 with modifications).

7.2.6 Missing Data

In general, data will be analyzed as received from the clinical database. Hence, except for some partial/missing dates (see below), missing values, including those caused by dropouts, will not be imputed. Missing or partially missing dates in the following situations will be imputed for purposes of analysis:

7.2.7 Partial/Missing Dates for Study-Related Visits or Procedures

It is anticipated that all study-related visit and procedure dates entered into the clinical study database will be complete (i.e. day, month, year are all recorded) and accurate. Any missing or partially missing

dates of this type will be queried before statistical analyses are performed. If the day, month, and/or year are still unknown, then the dates will be imputed as follows for purposes of analysis:

- If the day of the visit or procedure date is missing, then take the previous visit and add the target number of days to the next visit according to the visit schedule.
- If the month of the visit or procedure date is missing then take the previous visit and add the target number of months to the next visit according to the visit schedule.
- If the year of the visit or procedure date is missing, then the year will be queried. If the year is unknown, no imputation of year will take place.

Imputed dates will be flagged in the subject data listings.

7.2.8 Partial/Missing Dates for Adverse Events

For any adverse event that has a missing or incomplete start date, a query will be issued to capture the full date. If only a partial date is reported for the start of an AE, a complete date will be estimated using the following algorithm:

- If only the year is reported (i.e., missing the month and day): The date of the first dose of investigational product will be used as the start of the AE.
- The year and month are reported (i.e., missing the day): The first day of the month will be imputed.
- The month and day are reported (i.e., missing the year): only situations where the year is self-evident will be allowed.

No imputation will be applied to an incomplete AE end date. The rationale will be that there should be a start date for all subject AEs but there may not be an end dates for AEs that are ongoing at the time the subject exits the study.

7.3 Interim Analyses and Data Monitoring

7.3.1 Purpose of Interim Analyses

Other than the safety evaluation required to determine whether to proceed to Stage 2 of accrual, no planned formal interim analysis will be performed.

If concerns arise during any data reviews, the sponsor may request additional specific safety data be collected and recommend modifying study conduct.

7.3.2 Planned Schedule of Interim Analyses

As noted in Section 7.5.1, other than the safety evaluation required to determine whether to proceed to Stage 2 of accrual, no planned formal interim analysis will be performed.

7.3.3 Scope of Dose Escalation

In the event that attribution of causality of potential DLTs to study drug may be equivocal, discussions with the investigators, medical monitor and sponsor will occur and additional subjects may be enrolled at that dose level. Reviews will be conducted by the investigators, medical monitor and sponsor of all available safety data on an ongoing basis throughout the study. The study sponsor or its designee will notify the sites when enrollment into a dose level is complete and when the next dose level is open to enrollment during Stage 1.

The establishment of the MTD or the safety of the target RX-0201 dose of 250 mg/m2/day will be based on a review of the overall safety data by the investigators, medical monitor and sponsor. The MTD is the highest starting dose level associated with first-cycle DLTs in < 33.3% of subjects. Once the safety of the target RX-0201 dose of 250 mg/m2/day is initially established, additional subjects (up to 20 subjects total) will be enrolled to receive RX-0201 at the target RX-0201 dose of 250 mg/m2/day in Stage 2. Selection of a recommended Stage 2 starting dose from within the tested dose range will be based on evaluation of available safety information with findings regarding compliance.
Stopping Rules

The sponsor may also terminate the study at any time for reasons which may or may not be related to safety or study conduct.

7.3.4 Analysis Methods to Minimize Bias

None.

7.3.5 Adjustment of Confidence Intervals and p-values

Any statistical tests that are utilized will be two-sided, with a type 1 error rate of 5%. All confidence intervals will be two-sided, constructed at the 95% confidence level. Any inferential statistical tests conducted in this study will be considered exploratory in nature; therefore, no p-value adjustments for multiplicity analyses will be made.

Data will be summarized using the Safety Analysis Set with respect to enrollment and disposition summaries, demographics and baseline characteristics, concomitant medications, and safety measures. Summary (i.e. descriptive) statistics will include N, mean, standard deviation, median, range (minimum, maximum), values for continuous variables and frequencies, and percentages for categorical variables. Time-to-event analyses will be summarized using Kaplan-Meier survival analysis and graphs. 95% confidence intervals for the estimated median times and percentiles will also be displayed if applicable.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 7.4).

7.3.6 Interim Analysis for Sample Size Adjustment

Not applicable.

7.3.7 Practical Measures to Minimize Bias

Not applicable.

7.3.8 Documentation of Interim Analyses

Not applicable.

7.4 Multi-center Studies

Up to 20 sites in the US will participate in this study. Sites that do not enroll subjects within 3 months of site initiation may be terminated.

Data from all centers will be combined for the analysis purposes.

7.5 Multiple Testing

Not applicable.

8 Summary of Study Data

8.1 Subject Disposition

Subject enrollment by site and across all sites will be tabulated by dose group and all subjects.

The number of subjects discontinuing the study and the primary reason for discontinuation will be tabulated for descriptive purposes by dose group and overall.

Screen failure subjects will be included only in the disposition table and subject enrollment listing indicating reason for failure.

In addition, the number and percentage of subjects in each of the 4 analysis data sets (safety analysis set, full analysis set, per-protocol analysis set, and evaluable for tumor response analysis set,) will be summarized by treatment group.

8.2 Protocol Deviation

A protocol deviation will be any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP). The noncompliance may be either on the part of the subject, the investigator, or the study site staff. Protocol deviations will be identified and documented by Rexahn project management based on a review of data listings prior to database lock.

The number and percentage of subjects with any major and minor deviations will be tabulated for descriptive purposes by dose group and overall.

8.3 Demographic and Baseline Variables

A summary of age, gender, race, ethnicity, metastatic clear cell renal carcinoma diagnosis, tumor stage, current disease status, time (months) from first diagnosis of metastatic disease to screening visit, prior medical history, prior anti-cancer systemic therapy (related to study indication), prior anti-cancer radiotherapy (related to study indication), prior anti-cancer surgery (related to study indication), vital signs at screening, and ECOG Performance Status will be presented using appropriate descriptive statistics by dose group. The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using n, mean, median, standard deviation, and range (maximum, minimum).

8.4 Prior and Concomitant Medical Conditions

The number and percentage of all subjects with any medical history will be summarized overall and for each body system. Body systems will be included as recorded on the eCRF. Percentages will be calculated based on number of subjects in the safety analysis set.

Subjects' medical history data including medical condition, start date and end date/ongoing will be presented in a listing.

8.5 Prior and Concomitant Medications / Non-Drug Treatments

For the purpose of this analysis, concomitant medications/therapies will be defined as those medications/ therapies taken after the first administration of study drug; medications/therapies taken within 14 days prior to the first administration of study drug will be defined as prior medications/therapies. These medications will be coded using World Health Organization Drug Dictionary Enhanced (WHO Drug, June, 2014). The number and proportion of subjects in the safety analysis set using different prior/concomitant medications will be tabulated and summarized in a table by WHO Drug Anatomical-Therapeutic-Chemical (ATC) class and drug name for each dose group, and non-drug therapies will be mapped to preferred terms and related system organ classes (SOC) for each dose group. These data will also be presented in subject listings.

8.6 Treatment Compliance

Time on treatment (date of first dose to date of discontinuation date recorded on the end of study eCRF page) for each dose group will be characterized using descriptive summary statistics (n, mean, median, standard deviation, and range (maximum, minimum)).

RX-0201 compliance at each visit (%) = [Total Actual Volume Administered (mL) of RX-0201 / (Total reservoir volume of RX-0201)]*100

Everolimus at each visit (%) = (Number of Doses Taken / Number of Expected Doses)*100

A listing will be provided for the number and timing of prescribed dose reductions and dose interruptions.

Safety Analyses

The incidence of subjects with adverse events and clinical laboratory abnormalities, defined as dose limiting toxicities after 1 cycle of therapy, is one of the primary endpoints. The safety of RX-0201 will be evaluated through reporting using the grading system in the CTCAE version 4.03 for adverse events and laboratory abnormalities. This will be used to grade changes in vital signs, and laboratory assessments to include serum chemistry, hematology, coagulation tests and urinalysis. All statistical methods for safety data will be descriptive in nature.

Dose Limiting Toxicities that occur during Cycle 1 will be tabulated by DLT criteria and RX-0201 dose level. Vital signs will be tabulated and presented as raw data and change from baseline at each time point. Laboratory safety data will be tabulated in shift tables based on laboratory-specific normal ranges. Adverse events will be tabulated by body system, intensity and relationship to study drug.

Vital signs, weight, and data will be summarized using appropriate descriptive statistics, by treatment group and time.

All subjects who receive at least 1 dose of RX-0201 will be included in the final summaries and listings of safety data. All safety analyses will be performed by dose level, treatment cycle, and week, where appropriate.

8.7 Primary Safety Endpoint

One of the primary safety endpoints is the incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities (Stage 1).

8.8 Secondary Safety Endpoint

Incidence of adverse events, changes in clinical laboratory tests and vital signs over time (Stage 1 and Stage 2).

8.9 Extent of Exposure

Duration of exposure will be defined as the total number of days a subject is exposed to study drug and will be presented as the total number of days from the first dosing date (Day 1) to the last dosing date (date of last dose minus the date of first dose + 1).
The total cumulative dose will be defined as the sum of the received doses across all study days. The average daily dose and cumulative dose will be summarized by descriptive summary statistics.
A summary of each subject's exposure will be presented in a listing.

8.10 Adverse Events

All Adverse Events (AEs) will be listed as described on the eCRF.
An adverse event will be any untoward medical occurrence in a trial subject who is administered a drug or biologic (medicinal product) or who is using a medical device; the event does not necessarily have a causal relationship with study drug administration or usage.
For this protocol, untoward medical occurrences that should be reported as adverse events will include the following:

- Any unfavorable and unintended symptom, sign (including an abnormal laboratory finding), or disease temporally associated with the use of study drug, whether or not related to the study drug.

- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of study drug administration.
- Any complication that occurs as a result of a protocol-mandated procedure (e.g., venipuncture,) in the screening, study drug administration, or follow-up periods.
- Any injury or accident occurring during the screening, study drug administration, or follow-up periods. If a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.
- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Any laboratory (e.g., clinical chemistry, hematology, urinalysis) or investigational abnormality (e.g., X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test), or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin) should be recorded.
- A complication related to pregnancy or termination of a pregnancy (see Section 9.7.2 for additional information).

None of the following events will be considered an adverse event:

- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of overall laboratory monitoring.
- A diagnostic, medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion). However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy should be recorded in the subject's medical records and eCRFs.
- A pre-existing disease or condition or laboratory abnormality present or detected before the initial screening visit and that does not worsen.
- An intervention not associated with an untoward medical occurrence (e.g., hospitalization for elective surgery or for social and/or convenience reasons).
- An overdose without clinical sequela.

Verbatim terms of AEs will be mapped to preferred terms and related system organ classes (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1.The incidence rate of treatment emergent adverse events (TEAEs), defined as all adverse events reported as new or

worsened after the start of study drug, will be summarized by treatment group, system organ class, preferred term and maximum severity for all adverse events, serious adverse events, adverse events leading to discontinuation of study specified treatment, adverse events leading to discontinuation from the study and fatal adverse events using subjects in the safety population. In addition, summaries of exposure adjusted adverse event rates may also be presented. These summary tables will also be repeated for treatment related adverse events.

Tables will summarize the number and percentage of subjects having an event in each system organ class and preferred term by dose group. The denominator used to calculate incidence percentages consists of subjects receiving at least one dose of RX-0201 in the combination of RX-0201 and Everolimus group.

Further tables will summarize the number and percentage of subjects having adverse events, classified according to severity and the number and percentage of subjects with related events. The order of SOCs presented in tables will be according to the internationally agreed order of SOCs according to MedDRA. Within each SOC, the preferred terms will be shown in alphabetic order.

Note: Subjects who have multiple events in the same SOC and/or preferred term will be counted only once at each level of summation (overall, by SOC, and by preferred term) in the tables. For summaries of AEs by severity, only the highest severity of AE will be counted at each level of summation (overall, by SOC, and by preferred term) in the tables. For summaries of related AEs, subjects with more than one related AE will be counted only once at each level of summation (overall, by SOC, and by preferred term) in the tables.

8.11 Death, Serious Adverse Events and other Significant Adverse Events

A listing of subjects who died on study will be presented.

Tables will summarize the number and percentage of subjects having a serious adverse event in each SOC and preferred term. Further tables will summarize the number and percentage of subjects having serious adverse events judged to be related to RX-0201.

The order of SOCs presented in tables will be according to the internationally agreed order of SOCs according to Medical Dictionary for Regulatory Affairs (MedDRA) version 21.0. Within each SOC, the preferred terms will be shown in alphabetic order.

A listing of subjects reporting serious adverse events will be included.

A listing of subjects and the adverse events leading to study discontinuation will be presented.

Separate listings will be presented for total adverse events, serious adverse events, adverse events related to treatment with RX-0201 and CTCAE Grade 3 and 4 adverse events.

8.12 Pregnancies

Pregnancy Test results will be presented in by-subject listings for further medical review.

8.13 Clinical Laboratory Evaluations

Abnormal laboratory values will be assessed according to NCI CTCAE v4.03 where possible. The criteria for “clinically significant” laboratory abnormalities include a laboratory abnormality that leads to a DLT or a laboratory abnormality that results in any treatment-emergent therapeutic intervention (i.e., concomitant medication or therapy), or any other laboratory abnormality judged by the investigator to be of other particular clinical relevance.

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All relevant clinical laboratory tests will be classified as Low, Normal, and High, or Normal/Abnormal according to the normal ranges. This categorical data will be summarized in shift tables comparing the results at each scheduled post-baseline visit with those at the baseline visit.

When there are multiple values within a visit for a particular laboratory variable, the worst value will be taken (worst being the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold). If a subject has both a value below the threshold and a value above the threshold, the value furthest from the threshold will be chosen.

Urinalysis data will be presented in subject listings only.

All laboratory (hematology, coagulation, clinical chemistry, and urinalysis) parameters, values, units, normal range, flags collected (normal/abnormal) in the clinical database will be included in by-subject listings for further medical review. Laboratory values with associated CTCAE version 4 grades will have the associated grade displayed.

8.14 Other Safety Measures

8.14.1 ECOG Performance Status

ECOG performance status results will be summarized descriptively using N frequency and percentage by dose group at each visit.

8.14.2 Vital Signs

Resting vital signs, including pulse, blood pressure, respiration rate, temperature and weight, will be collected at screening, days 1, 8 and 15 of each cycle, end of treatment (or early termination), and safety follow-up visits. They will be summarized descriptively as will change from baseline results by treatment group and assessment time point.

9 Efficacy Analyses

9.1 Primary Efficacy Analysis

Tumor assessment(s) will be performed by the investigator using RECIST Version 1.1 criteria with modifications (Appendix E of the protocol) at the end of every 2 cycles

Subjects first meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a follow-up tumor assessment at the End of treatment or Early Termination visit providing it is ≥ 3 weeks from the previous tumor assessment.

The results will be available before the beginning of the next cycle. Radiographic tumor assessment(s) performed during the screening period will be used to prospectively identify all sites of disease present at the start of treatment. Subjects with symptoms suggestive of disease progression will be evaluated for tumor progression at the time symptoms occur.

The efficacy endpoints analyzed for this study are tumor response (complete response (CR) plus partial response (PR) according to RECIST), progression-free survival (PFS), time to response and response duration (for responders only). Progression-free survival is defined as time from first dose to the earlier of either first documented disease progression or death from any cause. Time to response is defined as time from first dose to first PR or CR (that is subsequently confirmed). Duration of response will be defined as time from first PR or CR (that is subsequently confirmed) to the earlier of either first documented disease progression or death from any cause.

9.1.1 Progression-Free Survival

Progression-free survival (PFS) will be defined as the date treatment starts to the date of first documented disease progression (PD) or death due to any cause, whichever comes first. Subjects alive without disease progression or lost to follow up at the time of analysis will be censored at the date of last response assessment. Table 1 below shows the censoring rules for progression-free survival.

The distribution of the progression-free survival will be estimated and graphed using Kaplan-Meier method. If applicable, estimates of the 25th percentile, median and 75th percentile and their respective 95% confidence intervals will be provided.

Kaplan-Meier curves for RX-0201 in combination with everolimus and everolimus alone will be estimated separately but displayed on one graph as a visual comparison of the survival curves between treatment groups. The log-rank test will be performed to compare the survival curves at the 0.05 significance level.

Table 1 Censoring Rules for Progression-Free Survival

Situation	End Date	Censored
Documented PD during the study	Date of the first assessment of the series of the tests that determined PD	No
Death during the study before PD	Date of death	No
Discontinued due to PD, but no documented PD	Date of observation of clinical progression (tumor timepoint response assessment CRF page) or date of discontinuation.	No
No baseline assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death, and no post-baseline tumor assessments	Date of randomization	Yes
Treatment discontinuation for other than PD or death with post-baseline tumor assessments	Date of last tumor assessment	Yes
Death or PD after two or more missed tumor assessments	Date of last tumor assessment before missed tumor assessment	Yes
Subjects still on treatment without PD as of data cut-off	Date of last tumor assessment	Yes
Only NE assessments after CR, PR, SD	Date of last tumor assessment before NE assessment	Yes

Note1: During the study includes Stage 2 treatment phase and follow-up period.

9.1.2 Best Overall Response (per eCRF)

Best overall response as assessed by the Investigator (with confirmation required for CR and PR) will be determined by RECIST criteria v1.1 per the eCRF and used in data display and analyses. The responses, listed from best to worst will be: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE).

The number and percentage of subjects in each category of best response and best Overall Response Rate (CR + PR) will be summarized for RX-0201 in combination with everolimus, and groups combined. The corresponding 95% confidence intervals will be computed by treatment group using the Clopper-Pearson method for calculating the exact binomial intervals.

9.1.3 Time to Response

Time to response is defined as time from first dose to first PR or CR (that is subsequently confirmed).

The distribution of time to response will be estimated and graphed using Kaplan-Meier method. If applicable, estimates of the 25th percentile, median and 75th percentile and their respective 95% confidence intervals will be provided.

Kaplan-Meier curves for RX-0201 in combination with everolimus will be estimated separately but displayed on one graph as a visual comparison of the survival curves between treatment groups. The log-rank test will be performed to compare the survival curves at the 0.05 significance level.

9.1.4 Duration of Response

Duration of response (DoR) will be defined as the time from the first documented response (CR or PR) to either the first documented disease progression or death due to any cause whichever is first.

Subjects achieving a CR or PR, who are alive without disease progression or are lost to follow up at the time of analysis, will be censored at the date of last response assessment.

Only subjects who achieve a best response of CR or PR by the confirmed Investigator Assessment of Efficacy will be included in this analysis. The duration of response will be assessed on a subject-by-subject basis and descriptively summarized by treatment group and overall.

Kaplan-Meier curves for RX-0201 in combination with everolimus will be estimated if applicable.

9.1.5 Pharmacokinetics

Pharmacokinetic parameters such as area under the time-concentration curve (AUC), maximum plasma concentration (Cmax), time to first maximum plasma concentration (Tmax), volume of distribution (Vd/F), terminal halflife (t1/2), and total body clearance (CL/F) will be estimated using standard non-compartmental methods and will be derived from blood plasma concentration versus time for RX-0201 for each subject.

RX-0201 concentrations in plasma will be listed by subject and time point. Concentrations by time data may be plotted for each subject. Pharmacokinetic parameters will be listed by subject and descriptively summarized by dose level. RX-0201 concentration time data will be summarized and plotted by dose group.

For the calculation of summary statistics of the concentration values, values that are below the limit of quantitation (BLQ) of 1.00 ng/mL are treated as 0.00 prior to the first quantifiable concentration and as missing thereafter.

10 Technical Details

Statistical Analysis Software (SAS) version 9.4 or later will be used to analyze the data, create summary tables, subject data listings, and graphical representation of the data.

All SAS programs will be validated via independent validation programs per H2O Clinical internal SOPs.

11 Summary of Changes to the Protocol

None.

12 References

International Federation of Pharmaceutical Manufacturers and Associations.Medical Dictionary for Regulatory Activities (MedDRA).Version 10.1.Reston, Virginia, USA; 2008.

WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary.July 2008 edition. Uppsala, Sweden; 2008.

SAS Institute Inc. SAS Version 9.1. Cary, NC, USA; 2002-2003.

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., & Verweij, J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer, 2009; 45: 228-247.

13 Listing of Tables, Listings and Figures

FIGURE NUMBER	FIGURE TITLE	POPULATION FOR ANALYSIS
1	Waterfall Plot (maximum % reduction from baseline in tumor size – target lesions only)	Evaluable for Tumor Response Analysis Set
2	Kaplan-Meier Plot – Progression Free Survival	Evaluable for Tumor Response Analysis Set
3	Kaplan-Meier Plot – Time to Response	Evaluable for Tumor Response Analysis Set
4	Kaplan-Meier Plot – Duration of Respons (if applicable)	Evaluable for Tumor Response Analysis

16 Appendices

Appendix A. Stage 1 Schedule of Assessments

	SCR[1]	Cycle 1			Cycle n[2]				EOT or ET Visit	SFU[3] Visit
		Day			Day					
Procedures and Treatments	-14	1	8	15	1	8	15	18-21		
Informed consent	X									
Medical and medication history	X									
Complete physical examination including weight and height	X									
ECOG performance status	X	X[4]			X[4]				X	X
Pregnancy test	X[5]	X[4, 6]							X	
Weight and BSA calculation (everolimus/RX-0201 arm only)		X[4]	X[18]		X[4]	X[18]				
Resting vital signs	X	X[4]	X[18]	X[18]	X[4, 16]	X[16, 18]	X[16, 18]		X	X
Hematology[7], chemistry[7], and coagulation[7, 16]	X	X[4]			X[4]				X	
Urinalysis[7]	X	X[4]			X[4, 16]				X	
Eligibility confirmation, randomization	X									
Everolimus administration[8]		X →	→	→	→	→	→	→		
Everolimus compliance[9]			X[18]	X[18]	X	X[18]	X[18]		X	
RX-0201 infusion (everolimus/RX-0201 arm only)		X →	→		X →	→				
RX-0201 compliance (everolimus/RX-0201 arm only)			X	X		X	X		X[10]	
Adverse events[11] and concomitant medication[16] assessment		X	X[18]	X[18]	X	X[18]	X[18]		X	X
Pharmacokinetic sampling				X[17]						
Disease assessment(s)	X[1]							X[12]	X[13]	
Biomarker blood sample		X[4]						X[14]	X[14]	
Archival Tumor Tissue		X[15]								
Tumor biopsy (optional)		X[4]								

Abbreviations: SCR = screening, ECOG = Eastern Cooperative Oncology Group, SFU = safety follow up visit; EOT = end of treatment visit; ET = early termination

1 Screening procedures will be performed within 14 days of enrollment/ randomization, except baseline tumor assessment, which can be evaluated within 21 days of enrollment/ randomization

2 Cycles 2 – 8 will follow the same assessment schedule

3 Safety follow-up visit will occur approximately 30 (+ 7) days after the last administration of RX-0201 or everolimus, whichever occurs later

4 Assessment can be performed within 3 days before Day 1 of each cycle

5 A serum pregnancy test must be negative for all females of childbearing potential

6 A urine pregnancy test must be negative for all females of childbearing potential before treatment begins. If a serum pregnancy test was done and determined negative within 72 hours of planned first dose a urine pregnancy test is not needed

7 Vital signs can be assessed up to 3 days before Day 1 and will be assessed whenever a PK sample is collected in Cycle 1

8 See Appendix C for analytes to be collected. If screening laboratory tests were performed within 72 hours of Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1. Samples to be taken before any RX-0201 or everolimus is administered9 Everolimus will be taken at the clinic on Days 1, 2, 15, and 16 of Cycle 1, and Day 1 of all other cycles

10 Subjects will bring all everolimus packaging (empty and full) to the clinic to determine drug compliance

11 RX-0201 compliance will be checked at the Early Termination if the subject was receiving RX-0201 at the time of early termination.

12 All adverse events attributed to study drug(s) will be assessed until resolution or return to baseline

13 Blood will be collected for subjects enrolled in only Stage 1 at the following time points:

- Immediately prior to Cycle 1 infusion, then at 1 hour ± 5 minutes, 2 hours ± 5 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes, and 24 hours (± 1 hour) (ie, Day 2) after start of RX-0201 infusion .
- Immediately prior to the end of Cycle 1 infusion (ie, Day 15), then at 1 hour ± 5 minutes, 2 hours ± 5 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes, and 24 hours (± 1 hour) (ie, Day 16) after the RX-0201 infusion pump has been turned off

14 Disease assessment will occur at the end of every 2 cycles

15 Subjects first meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a follow-up tumor assessment at the End of treatment or Early Termination visit providing it is ≥ 3 weeks from the previous tumor assessment in order to confirm the response based on RECIST ver. 1.1 criteria

16 Biomarker blood samples will be collected within 1 day of the disease assessment (approximately at the end of every 2 cycles and at EOT/ET if applicable)

17 Tissue blocks or tissue sections from initial diagnosis or upon diagnosis of advanced metastatic disease will be available for submission to the central laboratory within approximately 4 weeks after initiation of study treatment; exceptions require written documentation of why a sample is not available and prior approval by the sponsor before enrollment

Appendix B. Stage 2 Schedule of Assessments

	SCR[1]	Cycle 1			Cycle n[2]				EOT or ET	SFU[3]
		Day			Day				Visit	Visit
Procedures and Treatments	-14	1	8	15	1	8	15	18-21		
Informed consent	X									
Medical and medication history	X									
Complete physical examination including weight and height	X									
ECOG performance status	X	X[4]			X[4]				X	X
Pregnancy test	X[5]	X[4, 6]							X	
Weight and BSA calculation (everolimus/RX-0201 arm only)		X[4]	X[18]		X[4]	X[18]				
Resting vital signs	X	X[4]	X[18]	X[18]	X[4, 16]	X[16, 18]	X[16, 18]		X	X
Hematology[7], chemistry[7], and coagulation[7, 16]	X	X[4]			X[4]				X	
Urinalysis[7]	X	X[4]			X[4, 16]				X	
Eligibility confirmation, randomization	X									
Everolimus administration[8]		X →						→		
Everolimus compliance[9]			X[18]	X[18]	X	X[18]	X[18]		X	
RX-0201 infusion (everolimus/RX-0201 arm only)		X→			X→					
RX-0201 compliance (everolimus/RX-0201 arm only)			X	X		X	X		X[10]	
Adverse events[11] and concomitant medication[16] assessment		X	X[18]	X[18]	X	X[18]	X[18]		X	X
Pharmacokinetic sampling				X[17]						
Disease assessment(s)	X[1]							X[12]	X[13]	
Biomarker blood sample		X[4]						X[14]	X[14]	
Archival Tumor Tissue		X[15]								
Tumor biopsy (optional)		X[4]								

Abbreviations: SCR = screening, ECOG = Eastern Cooperative Oncology Group, SFU = safety follow up visit; EOT = end of treatment visit; ET = early termination

1 Screening procedures will be performed within 14 days of enrollment/ randomization, except baseline tumor assessment, which can be evaluated within 21 days of enrollment/ randomization
2 Cycles 2 – 8 will follow the same assessment schedule
3 Safety follow-up visit will occur approximately 30 (+ 7) days after the last administration of RX-0201 or everolimus, whichever occurs later
4 Assessment can be performed within 3 days before Day 1 of each cycle
5 A serum pregnancy test must be negative for all females of childbearing potential
6 A urine pregnancy test must be negative for all females of childbearing potential before treatment begins. If a serum pregnancy test was done and determined negative within 72 hours of planned first dose a urine pregnancy test is not needed
7 See Appendix C for analytes to be collected. If screening laboratory tests were performed within 72 hours of Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1. Samples to be taken before any RX-0201 or everolimus is administered
8 Everolimus (10 mg) will be taken at the clinic on Cycle 1 Day 1, and then at home every day thereafter
9 Subjects will bring all everolimus packaging (empty and full) to the clinic to determine drug compliance
10 RX-0201 compliance will be checked at the Early Termination if the subject was receiving RX-0201 at the time of early termination.
11 All adverse events attributed to study drug(s) will be assessed until resolution or return to baseline
12 Disease assessment will occur at the end of every 2 cycles
13 Subjects first meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a follow-up tumor assessment at the End of treatment or Early Termination visit providing it is ≥ 3 weeks from the previous tumor assessment in order to confirm the response based on RECIST ver. 1.1 criteria
14 Biomarker blood samples will be collected within 1 day of the disease assessment (approximately at the end of every 2 cycles and at EOT/ET if applicable)
15 Tissue blocks or tissue sections from initial diagnosis or upon diagnosis of advanced metastatic disease will be available for submission to the central laboratory within approximately 4 weeks after initiation of study treatment; exceptions require written documentation of why a sample is not available and prior approval by the sponsor before randomization