REVISION HISTORY

The table below describes revisions in Amendment 01 presented in the new protocol template (November 2016).

Revisions Per Amendment 01

Date: 01 May 2019

Change	Rationale	Affected Protocol Sections
Updated formal name of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).	The ICH changed its formal title in 2018.	• Title page (GCP statement) • Investigator signature page • Section 5.2
Clarified that the primary objective and endpoint is to evaluate ORR per investigator assessment.	Clarified that evaluation of ORR for the primary objective and endpoint will be per investigator assessment.	• Synopsis • 8.1 • 9.7.1.1.1 • 9.7.1.6.1
Clarified that the secondary objective and endpoint is to evaluate PFS per investigator assessment.	Evaluation of PFS for the secondary objective and endpoint will remain as per investigator assessment.	• Synopsis • 8.2 • 9.7.1.1.2 • 9.7.1.6.2
Added exploratory objectives and endpoints: To explore ORR based on IIR assessment. To explore PFS based on IIR assessment.	Added supportive exploratory endpoints per IIR to support the investigator assessed endpoints.	• Synopsis • 8.3 • 9.5.1.2 • 9.7.1.1.3 • 9.7.1.6.3
Added that the clinical benefit rate (CBR), disease control rate (DCR), and duration of response (DOR) endpoints will be explored per IIR assessment as well as per investigator.	Clarified that these exploratory endpoints will be determined based on both investigator and IIR assessments.	• Synopsis • 8.3 • 9.5.1.2 • 9.7.1.1.3 • 9.7.1.6.3
Added independent imaging review (IIR) for tumor assessment scans.	To strengthen data collection for potential regulatory submission of results from this open-label, single arm study.	• Synopsis • Section 9.5.1.2.1
Updated when to perform formal analyses of ORR, PFS, and OS.	Last patient in (LPI) plus 6 months will provide enough time to collect information for the primary and secondary endpoints and for efficacy and safety evaluation.	• Synopsis • Section 9.7.1.6.4

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-M001-221
Study Protocol Title:	A single-arm, multicenter, Phase 2 trial to evaluate efficacy and safety of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic non clear cell renal cell carcinoma (nccRCC) who have not received any chemotherapy for advanced disease
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA
Investigational Product Name:	Lenvatinib (E7080) and everolimus
Indication:	Non clear cell renal cell carcinoma
Phase:	Phase 2
Approval Date:	V1.0 13 May 2016 (Original Protocol) V2.0 01 May 2019 (Amendment 01)
IND Number:	124564
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080

Name of Active Ingredients: Lenvatinib and Everolimus

Study Protocol Title

A single-arm, multicenter, Phase 2 study to evaluate efficacy and safety of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic non clear cell renal cell carcinoma (nccRCC) who have not received any chemotherapy for advanced disease

Investigators

To be determined

Site(s)

Approximately 8 centers in the United States

Study Period and Phase of Development

Approximately 24 months, which include 18 months of enrollment and estimated 6 months of treatment

Phase 2

Objectives

Primary Objective

- To evaluate objective response rate (ORR), as assessed by the investigator, of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic non clear cell renal cell carcinoma (nccRCC) who have not received any chemotherapy for advanced disease

Secondary Objectives

The secondary objectives of the study are:

- To assess safety and tolerability of lenvatinib in combination with everolimus
- To evaluate progression-free survival (PFS) as assessed by the investigator
- To evaluate overall survival (OS)
- To assess the pharmacokinetic (PK) profiles of lenvatinib and everolimus during combination therapy in subjects with nccRCC

Exploratory Objectives

- To explore ORR as assessed by independent imaging review (IIR)
- To explore PFS as assessed by IIR
- To explore clinical benefit rate (CBR) as assessed by the investigator and by IIR
- To explore disease control rate (DCR) as assessed by the investigator and by IIR
- To explore duration of response (DOR) as assessed by the investigator and by IIR
- To identify and explore tumor and blood biomarkers that correlate with clinical outcomes, including efficacy
- To explore the relationship of population PK derived exposure parameters to biomarker, safety, and efficacy data using a model-based approach

Study Design

This is a single-arm, multicenter, Phase 2 study of lenvatinib in combination with everolimus (lenvatinib 18 mg/day + everolimus 5 mg/day) in subjects with unresectable advanced or metastatic nccRCC who have not received any chemotherapy for advanced disease. A Simon's Two-Stage Design will be implemented in approximately 31 enrolled subjects. Sixteen subjects will be enrolled in Stage 1. If there are at least 2 responders as assessed by ORR, the study will proceed to Stage 2 in which 15 more subjects may be enrolled. Otherwise, the study will stop early for futility. In the final analysis of 31 subjects, at least 6 responders are required to show a statistically significant improvement of ORR over historical control in the same patient population.

This study consists of 3 Phases: a Pretreatment Phase (Screening and Baseline Periods), a Treatment Phase (starting Cycle 1, Day 1), and a Posttreatment Phase (End of Treatment Visit and survival Follow-up).

The **Pretreatment Phase** will last no longer than 21 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to treatment.

The **Treatment Phase** will begin at the time of study drug administration on Day 1 of Cycle 1 and continue in 28-day (4-week) cycles until completion of the off-treatment assessments (within 30 days after the last study drug administration). Lenvatinib 18 mg/day and everolimus 5 mg/day will be administered orally. Subjects will undergo safety and efficacy assessments. Toxicity will be managed by treatment interruption, dose reduction and/or treatment discontinuation. Subjects who discontinue one of the study drugs due to its toxicities may continue to receive the other study drug as long as they demonstrate clinical benefit. Subjects will discontinue both study drugs at the time of confirmed disease progression, development of unacceptable toxicity, withdrawal of consent, or study termination by the sponsor.

The **Posttreatment Phase** will start at the End of Treatment Visit and will continue as long as the subject is alive or until the study subject withdraws consent. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessment every 8 weeks ±1 week until documentation of disease progression or start of another anticancer therapy. Follow-up assessment for survival will be performed every 12 weeks ±1 week.

Number of Subjects

A total of approximately 31 subjects will be enrolled.

Inclusion Criteria

1. Males or females age ≥ 18 years at the time of informed consent form (ICF).
2. Histologically confirmed nccRCC who have not received any chemotherapy for advanced disease. Subjects must have one of the following subtypes of nccRCC: papillary, chromophobe, collecting duct carcinoma (CDC), renal medullary carcinoma (RMC), or unclassified.
3. Radiologically measurable disease meeting the following criteria:
   a. At least 1 lesion of ≥ 10 mm in the longest diameter for a nonlymph node or ≥ 15 mm in the short axis diameter for a lymph node which is serially measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Appendix 1) using computerized tomography (CT) or magnetic resonance imaging (MRI).
   b. Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of subsequent progressive disease (substantial size increase of ≥20%) to be deemed a target lesion.
4. Eastern Cooperative Oncology Group (ECOG) (Appendix 2) performance status of 0 to 1.

5. Blood pressure (BP) ≤ 140/90 mmHg at Screening with or without antihypertensive medications and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1.
6. Adequate renal function as evidenced by calculated creatinine clearance ≥ 30 mL/minute according to the Cockcroft and Gault formula (Appendix 3).
7. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L and
    b. Hemoglobin ≥ 10.0 g/dL (can be corrected by growth factor or transfusion prior to first dose of study drug) and
    c. Platelet count ≥ 100×10^9/L
8. Adequate liver function:
    a. Bilirubin ≤ 1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome
    b. Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if subject has liver metastases). If ALP is > 3 × ULN (in the absence of liver metastases) or > 5 × ULN (in the presence of liver metastases) AND subjects are also known to have bone metastases, the liver-specific ALP must be separated from the total and used to assess the liver function instead of the total ALP.
9. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

Exclusion Criteria

1. Predominant clear cell renal cell carcinoma (RCC)
2. Prior anticancer chemotherapy or targeted therapy for advanced nccRCC.
3. Prior exposure to lenvatinib or mammalian target of rapamycin (mTOR) inhibitor.
4. Known intolerance to lenvatinib, everolimus (or other rapamycin derivatives), or any of the excipients.
5. Major surgery performed within 3 weeks prior to the first dose of study drugs or scheduled for major surgery during the study.
6. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib or everolimus.
7. Subjects having > 1 + proteinuria on urine dipstick testing will undergo 24 hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥ 1 g/24 hours will be ineligible.
8. Fasting total cholesterol >300 mg/dL (or >7.75 mmol/L) or fasting triglycerides level >2.5 × ULN. NOTE: these subjects can be included after initiation or adjustment of lipid-lowering medication.
9. Uncontrolled diabetes as defined by fasting glucose > 1.5 times the ULN. NOTE: In case this threshold is exceeded, these subjects can only be included after initiation or adjustment of glucose-lowering medication.
10. Known history of, or any evidence of, interstitial lung disease or active noninfectious pneumonitis.
11. Significant cardiovascular impairment: History of (a) congestive heart failure greater than New York Heart Association (NYHA) (Appendix 4) Class II, (b) unstable angina, (c) myocardial infarction (d) stroke, or (e) cardiac arrhythmia associated with hemodynamic instability within 6

months of the first dose of study drugs.

12. Prolongation of QTcF interval to >480 msec.
13. Known history of human immunodeficiency virus (HIV) positive.
14. Known active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (eg, hepatitis C virus [HCV] RNA detected).
15. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.
16. Subjects with central nervous system (CNS) (eg, brain or leptomeningeal) metastases.
17. Other active malignancy (except definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within past 24 months.
18. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG or hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
19. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as a condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from being sexually active during the study period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study or for 28 days after study drug discontinuation.
    - Are using oral hormonal contraceptives and who do not agree to add a barrier method.
    - (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).
20. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period and for 28 days after study drug discontinuation.
21. Evidence of clinically significant disease (eg, cardiovascular, respiratory, gastrointestinal, renal, or infectious disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
22. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
23. Active and current use of illegal recreational drugs.

24. Currently enrolled in another interventional clinical study or used any investigational drug or device within the past 28 days preceding informed consent.

Study Treatments

Lenvatinib will be provided as 4 mg and 10 mg capsules and everolimus will be provided as 5 mg tablets.

Initial doses of lenvatinib 18 mg/day (one 10-mg capsule and two 4-mg capsules) and everolimus 5 mg/day are to be taken orally in immediate succession once a day (QD), recommended approximately at the same time each morning (consistently either with or without food).

If a subject cannot tolerate lenvatinib due to its toxicities, the lenvatinib dose may be reduced, interrupted or discontinued according to the guidelines provided in Table 1 and Table 2. Lenvatinib dose reductions occur in succession based on the previous dose level, ie, one level at a time from 18 mg/day to 14, 10, and 8 mg/day. Any dose reduction below 8 mg/day must be discussed with the sponsor.

If a subject cannot tolerate everolimus due to its toxicities, the everolimus dose may be reduced, interrupted or discontinued. Everolimus dose may be reduced from 5 mg/day to 5 mg every other day.

Dose adjustments for both study drugs will be made according to the guidelines provided in Table 2 for management of intolerable toxicities. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required. Once the dose has been reduced, it cannot be increased at a later date.

Subjects who are discontinued from one of the study drugs due to intolerance to that drug may continue to receive the other study drug as long as they demonstrate clinical benefit.

Refer to appropriate protocol section for management of hypertension (Section 9.4.1.1.1), proteinuria (Section 9.4.1.1.2), hepatic injury (Section 9.4.1.1.3), thromboembolic events (Section 9.4.1.1.4), posterior reversible encephalopathy syndrome (PRES) (Section 9.4.1.1.5), hypocalcemia (Section 9.4.1.1.6), noninfectious pneumonitis (Section 9.4.1.1.7), infections (Section 9.4.1.1.8), and blood glucose/lipids (Section 9.4.1.1.9) before consulting the table below, as appropriate.

Table 1 Dose Reduction Recommendations for Lenvatinib in Combination With Everolimus

Initial Lenvatinib Dose (mg, QD)	Adjusted Dose To Be Administered (mg, QD)			
	Reduction 1	Reduction 2	Reduction 3	Reduction 4
18	14	10	8	a

QD = once daily.
a: Consult Sponsor for further dose reduction recommendations.

Table 2 Lenvatinib-Everolimus Combination Therapy Dose Reduction and Interruption Instructions[a]

Lenvatinib/Everolimus Treatment-Related Toxicity[b,c] Including Hepatic Injury and Thromboembolic Events	During Therapy	Adjusted Dose
Grade 1 Tolerable Grade 2		

	Continue treatment	No change
Intolerable Grade 2[c]		
First occurrence	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1	Dose reduction of lenvatinib (one dose reduction level, see Table 1 above) and, if combination dosing, resume everolimus at the same dose as prior to dose interruption.
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1	Dose reduction of lenvatinib (one dose reduction level, see Table 1 above) and, if combination dosing, resume everolimus at the same dose as prior to dose interruption.
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1	Dose reduction of lenvatinib (one dose reduction level, see Table 1 above) and, if combination dosing, resume everolimus at the same dose as prior to dose interruption.
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1	Discuss with sponsor
Grade 3[d,e]		
First occurrence	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1[f]	Dose reduction of lenvatinib (one dose reduction level, see Table 1 above) and, if combination dosing, resume everolimus at the same dose as prior to dose interruption.
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1 o[f]	Investigator to decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs was required. Dose reduction of lenvatinib (one dose reduction level, see Table 1 above) and/or reduce everolimus to 5 mg every other day.
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1[f]	Investigator to decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs was required. Dose reduction of lenvatinib (one dose reduction level, see Table 1 above) and/or adjust everolimus as follows: i) if 5 mg daily everolimus at event onset, reduce to 5 mg every other day, or ii) if 5 mg every other day everolimus at event onset, discontinue.
Fourth occurrence	Interrupt lenvatinib and everolimus	Discuss with sponsor
Grade 4[g]: Discontinue lenvatinib and everolimus		
Note: For grading see Common Terminology Criteria (CTC) for Adverse Events (AE) version 4.03 (Appendix 5). Collect all CTC grades of AEs, decreasing and increasing grade. a: A delay of lenvatinib/everolimus treatment for more than 28 days (due to lenvatinib/ everolimus-related toxicities) requires a discussion with the sponsor before treatment may be resumed. b: Excluding alopecia. Drug interruption and dose reduction may be initiated for intolerable Grade 2 and Grade 3		

related symptoms such as anemia, lymphocytopenia, asymptomatic neutropenia if there are no other treatment options available and the investigator considers that dose interruption or reduction of study medication is the only remaining alternative. Optimal medical management for nausea, vomiting, and/or diarrhea have to be initiated prior to any lenvatinib/ everolimus interruption or dose reduction.

c: Applicable only to Grade 2 toxicities judged by the subject and physician to be intolerable. If Grade 2 toxicity is determined to be intolerable, the dose of study drug will be reduced with or without dose interruption. Interruption for Grade 3 toxicities is mandatory.

d: Obese subjects with weight loss requiring dose interruption and reduction do not need to return to Baseline or Grade 1 weight loss to restart lenvatinib. Based on the judgment of the investigator, subjects may be restarted at the lower dose of lenvatinib once the weight has been stable for at least 1 week. Normal body mass index (BMI) should be used as the new baseline for future dose reductions.

e: Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator (eg, alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyl transpeptidase [γ-GTP] values < 10 × upper limit of normal [ULN], and Na).

f: For hematology toxicities, restart treatment after toxicity resolves to Grade 2.

g: Excluding laboratory abnormalities judged to be nonlife-threatening, in which case have to be managed as Grade 3.

Management of Hypertension

Lenvatinib-everolimus combination therapy should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP significantly ≥ 160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the BP is controlled, lenvatinib-everolimus combination therapy should be resumed as described below.

The following guidelines should be followed for the management of systolic BP ≥ 140 mmHg up to < 160 mmHg or diastolic BP ≥ 90 mmHg up to < 100 mmHg confirmed on repeat measurements after an hour, for subjects receiving lenvatinib-everolimus combination therapy:

- Continue lenvatinib-everolimus combination therapy and institute antihypertensive therapy for subjects not already receiving this.
- For subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.

The following guidelines should be followed for the management of systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg confirmed on repeat measurements after an hour, for subjects receiving lenvatinib-everolimus combination therapy:

- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib-everolimus combination therapy administration should be interrupted and restarted when BP ≤ 150/95 mmHg at a dose of: one level of dose reduction (ie, 14-mg once daily) per Table 2 of lenvatinib. Resume everolimus at the same dose as prior to dose interruption.
    - If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the first reduced dose (ie, 14-mg once daily) despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib-everolimus combination therapy administration should be interrupted and restarted when BP ≤ 150/95 mmHg at a dose of: one level of dose reduction (ie, 10-mg once daily) per Table 1 and Table 2 of lenvatinib. Resume everolimus at the same dose as prior to dose interruption.
    - If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the next reduced dose (ie, 10-mg once daily) despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib-everolimus combination therapy administration

should be interrupted and restarted when BP ≤ 150/95 mmHg at a dose of: one level of dose reduction (ie, 8-mg once daily) per Table 1 and Table 2 of lenvatinib. Resume everolimus at the same dose as prior to dose interruption.

- Additional dose reduction should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management.
- Discontinue lenvatinib-everolimus combination therapy.

Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Visits and Procedures/Assessments. Guidelines for assessment and management of proteinuria are summarized as follows for subjects receiving lenvatinib-everolimus combination therapy:

- Initial episode of proteinuria: if proteinuria ≥ 2+ is detected on urine dipstick testing, lenvatinib-everolimus combination therapy will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Grading according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03) will be based on the 24-hour urinary protein result. Management of lenvatinib-everolimus combination therapy will be based on the grade of proteinuria according to the Dose Reduction and Interruption Instructions (Table 2). Where lenvatinib-everolimus combination therapy is interrupted and restarted, everolimus should resume at the same dose as prior to dose interruption and not as instructed in Table 2.
- Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+, trace, or negative for 3 consecutive months. Any subsequent increases in the level of proteinuria ≥2+ on urine dipstick testing must be confirmed with a 24-hour urinary protein test, which will be assessed and graded, and continued management of lenvatinib-everolimus combination therapy administration will be based on the Dose Reduction and Interruption Instructions (Table 2). Where lenvatinib-everolimus combination therapy is interrupted and restarted, everolimus should resume at the same dose as prior to dose interruption and not as instructed in Table 2. If a new event of proteinuria ≥ 2+ occurs, the subject must resume urine dipstick testing for evaluation of proteinuria every 2 weeks until results are 1+, trace, or negative for 3 consecutive months.

Management of Hepatotoxicity

Regular monitoring of liver function tests (ALT, AST, bilirubin levels) should be conducted as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in the Dose Reduction and Interruption Instructions (Table 2) should be followed. Appropriate supportive care should be provided along with close monitoring. If hepatic failure occurs the lenvatinib-everolimus combination therapy must be discontinued.

Management of Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, signs of deep vein thrombosis (DVT) including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Dose Reduction and Interruption Instructions (Table 2) should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, lenvatinib-everolimus combination therapy must be discontinued.

Management of Posterior Reversible Encephalopathy Syndrome
In clinical studies with lenvatinib, events of PRES were reported in less than 1% of lenvatinib-treated subjects. PRES is a neurological disorder, which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. An MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control BP. If subject develops PRES, contact study sponsor.

Management of Hypocalcemia

Serum calcium should be monitored at least monthly and replace calcium as necessary during lenvatinib treatment. Interrupt and adjust lenvatinib dosing as necessary depending on severity, presence of electrocardiogram (ECG) changes, and persistence of hypocalcemia.

Management of Noninfectious Pneumonitis
Noninfectious pneumonitis is a recognized class effect of rapamycin derivatives, including everolimus. Noninfectious pneumonitis (including interstitial lung disease) was described in 12% of subjects taking everolimus. Some cases were severe and on rare occasions, a fatal outcome was observed. Investigators should therefore consider a diagnosis of noninfectious pneumonitis in subjects presenting with nonspecific respiratory signs and symptoms and in whom infectious, neoplastic and other nonmedicinal causes have been excluded by means of appropriate investigations.

Guidelines for assessment and management of noninfectious pneumonitis are summarized as follows for subjects receiving lenvatinib-everolimus combination therapy:

- Subjects who develop radiological changes suggestive of noninfectious pneumonitis and have few or no symptoms (CTCAE grade 1) may continue lenvatinib-everolimus combination therapy without dose adjustments.
- If symptoms are CTCAE grade 2:
    - Starting dose of lenvatinib combination therapy with 5 mg daily everolimus: combination therapy should be interrupted and the use of corticosteroids may be indicated until symptoms abate (resolved to CTCAE Grade 0-1 or baseline) and may be restarted with 5 mg everolimus daily in combination with lenvatinib (ie, lenvatinib reinitiated at the same dose as prior to dose interruption) administered daily. Discontinue everolimus if failure to recover within 4 weeks of reinitiating treatment, and continue lenvatinib as a single agent therapy depending on individual clinical circumstance.
    - If Grade 2 noninfectious pneumonitis recurs despite optimal management, then lenvatinib-everolimus combination therapy administration should be interrupted and the use of corticosteroids may be indicated until symptoms abate (resolved to CTCAE Grade 0-1 or baseline). Lenvatinib may be reinitiated as a single agent therapy depending on individual clinical circumstances.
- If symptoms are CTCAE Grade 3:
    - Starting dose of lenvatinib combination therapy with 5 mg daily everolimus: combination therapy should be interrupted and the use of corticosteroids may be indicated until clinical symptoms resolve. Lenvatinib may be reinitiated as single agent therapy depending on the individual clinical circumstances.
- If symptoms are CTCAE grade 4:
    - Study medications should be discontinued.

Management of Infections

Everolimus has immunosuppressive properties and may predispose subjects to infections. Therefore, monitor for signs and symptoms of infection and treat promptly. Dose alterations of everolimus (either as single agent or in lenvatinib-everolimus combination therapy) may be required in

accordance with prescribing information.

Management of Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia and hypertriglyceridemia are recognized class effects of rapamycin derivatives, including everolimus. Glycemic control should be optimized before starting a subject on this study.

Blood glucose will be monitored as specified in the Schedule of Visits and Procedures/Assessments. For subjects with blood glucose > ULN, a fasting (> 6 hours, water only) blood glucose sample will be obtained. Grading according to CTCAE will be based on the fasting blood glucose result. Insulin and/or oral hypoglycemic agents may have to be introduced (or the dose increased) to control blood glucose levels. The choice of hypoglycemic agent should be individualized to the subjects' clinical circumstances and follow standard medical practice in addition to consideration of avoiding coadministration of everolimus with inhibitors and inducers of cytochrome P450 (CYP) 3A4 and/or the multidrug efflux pump P-glycoprotein (PgP).

Dose alterations of everolimus (either as single agent or in lenvatinib-everolimus combination therapy) may be required in accordance with prescribing information. Where lenvatinib-everolimus combination therapy is interrupted, lenvatinib should resume at the same dose as prior to dose interruption.

Duration of Treatment

Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor discontinuation. The duration of treatment for each subject is estimated to be approximately 6 months.

Concomitant Drug/Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of ICF) until 28 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with the study drugs may be continued during the study.

Treatment of complications or adverse events (AEs), or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study drugs.

Aspirin, nonsteroidal anti-inflammatory drugs, and low-molecular-weight heparin are permissible but should be used with caution. Granulocyte colony-stimulating factor or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts.

If concomitant medication/therapy is administered for an AE, investigators will record that AE on the Adverse Events Case Report Form (CRF).

Subjects should not receive other antitumor therapies while on study. If subjects receive additional antitumor therapies during the study, such as radiotherapy, other chemotherapy, or immunotherapy, this will be judged to represent evidence of disease progression, and continuation of study medication should be discussed with the sponsor. Following this discussion, if the joint decision is made to discontinue study treatment, then such subjects will complete all End of Treatment assessments and continue to be followed for survival in the Follow-Up Period.

Assessments

Efficacy Assessments

The primary endpoint (ORR), secondary endpoint (PFS), and exploratory endpoints (CBR, DCR, and DOR) will be evaluated by the investigator. In addition, ORR, PFS, CBR, DCR, and DOR will be assessed by IIR. The OS status will be assessed throughout the study.

Tumor assessments will be performed using RECIST v1.1. Investigator-determined response assessments are to be performed at the site by appropriately qualified personnel at each time point and recorded on the appropriate CRFs. All tumor assessment scans will be sent to an imaging core laboratory specified by the sponsor for quality assessment and independent imaging review. Tumor assessments will be carried out following the guidelines provided by the imaging core laboratory. Historical scans performed within the Screening period that do not follow the guidelines completely may be used to demonstrate eligibility, as long as they meet minimum standards as separately defined by the imaging core laboratory.

Tumor assessments including a CT chest and CT or MRI of the abdomen and pelvis, and other areas of known or newly suspected disease should be performed prior to Baseline (between Day –28 to Day -2) and every 8 weeks (within the 8th week) from the date of first dose during the Treatment Phase. A brain scan will be performed at Screening, and thereafter if clinically indicated. A bone scan will be performed during the pretreatment phase to establish a baseline (a historical bone scan performed within 6 weeks before first dose is acceptable), every 24 weeks, and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging.

In subjects with complete response (CR) based on body CT/MRI scans, bone scan and brain scan, assessment will be required at response confirmation. All objective responses must be confirmed at least 28 days following the initial achievement of response. Subjects going off study treatments without disease progression in the Treatment Phase will continue to undergo tumor assessments according to the above schedule until disease progression is documented or another anticancer therapy is initiated.

Pharmacokinetic Assessments

Sparse PK samples will be collected from all subjects and will be analyzed using the population approach. A total of 12 samples (6 plasma samples for lenvatinib and 6 whole blood samples for everolimus) per subject will be obtained at the following time points: 2 to 8 hours postdose on Cycle 1 Day 1 (C1D1), prior to dose on Cycle 1 Day 15 (C1D15), prior to dose and 2 to 8 hours postdose on Day 1 of Cycles 2 and 3.

Pharmacodynamic, Pharmacogenomics, and Other Biomarker Assessments

Blood and Tissue Biomarkers: Biomarker discovery and/or validation may be performed to identify blood or tumor biomarkers that may be useful to predict subject response to study drug, evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. In addition, biomarkers identified in other clinical studies of study drug may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

A blood sample for pharmacodynamic and exploratory biomarker analysis will be collected predose on Day -1 or C1D1, on C1D15, and on Day 1 of subsequent cycles (during Treatment Phase), and at the End of Treatment assessment. Blood samples from all consented subjects may undergo analyses including, but not limited to, global proteomic and/or enzyme-linked immunosorbent assay (ELISA)-based analyses or multiplex bead-based immunoassay in an effort to assess pharmacodynamic biomarkers.

Pharmacogenomic (PG) Assessments: Archived, fixed tumor tissue will be collected (if available)

from all subjects for potential assessment of mutations and other genetic alterations or genes and/or proteins that may be important in the development and progression of cancer as well as in response to study drug treatment for potential use in diagnostic development. Appropriate technology/methodologies will be used based on the amount of tumor tissue available.

A blood sample for peripheral blood mononuclear cells (PBMC) and plasma isolation will be collected from consented subjects for potential analysis of cell free nucleic acid (cf-nucleic acid) analysis and exploratory immune cell analysis. Cell free nucleic acid isolated from plasma samples may be used to obtain circulating tumor DNA (ctDNA) and explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment. PBMCs may be used for immune cell profiling (eg. tumor infiltrating lymphocytes, T-cell repertoire, and immune cell types).

A blood sample will be collected for pharmacogenomics (PG) analysis (except where prohibited by regional or local laws). Variation in lenvatinib exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data. Genomic deoxyribonucleic acid (DNA) extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor and for potential profiling of immune cells.

Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib, cancer and/or for potential diagnostic development.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Safety Assessments

General safety will be assessed by the monitoring and recording of all AEs and serious adverse events (SAEs), regular monitoring of hematology and blood chemistry, regular measurement of vital signs, ECG, and the performance of physical examinations (PE) and other safety assessments in line with local regulations governing a study of this nature.

Progression of nccRCC and signs and symptoms clearly related to the disease progression should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

In case of life-threatening bleeding, the investigator should discuss the case with the Eisai Medical Monitor, in addition to discontinuing lenvatinib per Synopsis Table 1 for Grade 4 toxicity and treat the subject based on the institution's standard practice. Clinically significant bleeding will be considered as study-specific events and should always be considered as serious important medical events, which will be entered on the adverse event CRF and reported using the procedures for reporting SAEs, even if the study-specific event does not meet other serious criteria.

Bioanalytical Methods

Lenvatinib in plasma and everolimus in blood will be quantified using validated high pressure liquid chromatography (HPLC)-tandem mass spectroscopy methods.

Statistical Methods

Study Endpoints

Primary Efficacy Endpoint

- The primary efficacy endpoint is ORR based on investigator assessment, defined as the

proportion of subjects who have a best overall response (BOR) of CR or PR.

Secondary Efficacy Endpoints

- Progression-free survival (PFS) based on investigator assessment – defined as the time from date of first dose of study drug to date of first documentation of disease progression or death, whichever occurs first.
- Overall survival (OS) – defined as the time from the date of first dose of study drug until date of death from any cause.

Exploratory Endpoints

- ORR based on IIR assessment
- PFS based on IIR assessment
- Clinical benefit rate (CBR) is the proportion of subjects who have a BOR of CR or PR or durable stable disease (SD). Stable disease must be achieved at ≥ 23 weeks after first lenvatinib administration to be considered durable SD. The CBR will be determined based on both investigator and IIR assessment.
- Disease control rate (DCR) is the proportion of subjects who have a BOR of CR, PR or SD. The DCR will be determined based on both investigator and IIR assessment.
- Duration of response (DOR) is defined as the time from the date that the criteria are met for CR or PR (whichever is recorded first) to the date that progressive disease (PD) is objectively documented or death, whichever occurs first. The DOR will be determined based on both investigator and IIR assessment.

Analysis Sets

The Full Analysis Set (FAS) includes subjects who received at least 1 dose of the study drugs. This will be the analysis set for all efficacy and safety evaluations.

The Evaluable Analysis Set (EAS, a subset of the FAS) includes all subjects who have both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless the subjects are discontinued because of disease progression or toxicity. This will be used for the sensitivity analyses of efficacy.

The Pharmacokinetic Analysis Set will include all subjects who received at least one dose of study drug and have evaluable lenvatinib plasma and/or everolimus whole blood concentration data.

The Pharmacodynamic Analysis Set will include all subjects who received at least one dose of study drug and have evaluable pharmacodynamics data.

Efficacy Analyses

Primary efficacy analyses

Primary endpoint ORR assessed by investigator review will be analyzed using the FAS. Subjects who did not have a tumor assessment for any reason will be considered as nonresponders and included in the denominator when calculating response rate.

In this population, ORR in the historical control is assumed to be 8% (Hudes, et al., 2007). The ORR in this study is estimated as 25%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H_0: ORR=8%

H_a: ORR ≥25%

Simon's Two-Stage Design (Simon, 1989) is used in hypothesis testing for the primary endpoints. The interim futility analysis after Stage 1 allows for an early evaluation of efficacy results in order to stop the study early in the case of low anticancer activity. A minimum of 2 responders as assessed by

ORR in the Stage 1 subjects (n_1=16) is required in the interim analysis for the study to proceed to Stage 2 in which 15 more subjects may be enrolled. In the final analysis of ORR, a minimum of 6 responders is required in Stages 1 and 2 subjects combined (n=31) to claim the superiority of study treatment over historical controls.

Simon's Two-Stage Design for Interim Futility and Final Analyses of ORR

	Threshold
Interim Analysis	Continue if ≥2 responders when n_1=16
Final Analysis	Reject H_0 if ≥6 responders when n=31

Secondary efficacy analyses

PFS assessed by the investigator and OS will be analyzed using Kaplan–Meier product-limit estimates. Median PFS and OS and the cumulative probability of PFS at 3, 6, and 12 months and cumulative probability of OS at 6, 12, and 18 months will be presented with two-sided 95% confidence interval (CI) if estimable. PFS censoring rules will follow Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

The cumulative PFS and OS will be plotted over time. The median, first, and third quartiles from Kaplan–Meier estimation for PFS and OS will be provided with 95% CI if estimable.

Exploratory efficacy analyses

The ORR based on IIR assessment will be evaluated using the same method described in the primary analysis.

A 2-sided Clopper–Pearson 95% CI will be constructed for CBR and DCR. The DOR and PFS based on IIR assessment will be analyzed using time to event methods described above.

Formal analyses of ORR, PFS and OS

A formal analysis will be carried out after all subjects have been enrolled and on study treatment for at least 6 months or have discontinued due to disease progression, death or toxicity. Since the primary endpoint ORR data are expected to be observed sooner than the secondary endpoints, the timing of the formal analysis is chosen such that the secondary endpoints, PFS and OS, will be adequately described. The primary population for efficacy and safety analyses is the FAS.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

A population PK approach will be used to characterize the PK of lenvatinib and everolimus and the final PK model will be used to derive lenvatinib and everolimus exposure parameters to be used in the subsequent pharmacokinetic (PK)/pharmacodynamic analyses. The analyses will be detailed in a separate analysis plan. Concentrations of each analyte will be graphed by time within each nominal collection interval. Average dose at each collection interval will also be displayed.

Pharmacokinetic/Pharmacodynamic Analyses

Lenvatinib and everolimus exposure parameters derived from the population PK analysis will be related to biomarker, safety, and efficacy data using a model-based approach. For some PK/ pharmacodynamic analyses, data from this study may be pooled with data from other clinical studies of study drug.

For efficacy, a tumor growth inhibition model based on longitudinal tumor size measurements of

target lesions will be included. We plan to explore exposure to both lenvatinib and everolimus exposure and/or selected biomarkers, identified in other studies of study drug, as predictors and/or correlations with tumor burden changes in the tumor growth inhibition model. Other analyses will include logistic regression analysis for ORR_{24W}.

For the exposure-response relationship of safety, data will be analyzed using a longitudinal categorical logistic regression analysis for AEs leading to dosing reduction or interruption.

For the exposure-response relationship for selected biomarkers, identified in other clinical studies of study drug, data may be analyzed using a model-based approach.

Population PK and PK/pharmacodynamic analyses will be detailed in a separate analysis plan.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Soluble, tissue, genetic and/or imaging biomarkers (Baseline and/or posttreatment) may be summarized using descriptive statistics and correlated with clinical outcomes-related endpoints for safety and/or efficacy as appropriate. Details will be included in a separate analysis plan.

Safety Analyses

Safety, using the FAS, will be assessed by monitoring and recording of all AEs including all CTCAE grades, regular monitoring of hematology and clinical chemistry, urinalysis, regular measurement of vital signs, 12-lead ECGs, and performance of PEs.

Adverse events and other clinical safety data will be summarized descriptively in the FAS. The incidence of treatment-emergent adverse events (TEAEs), SAEs, drug-related AEs and AEs leading to discontinuation will be summarized in tabulation. Hematology, serum chemistry, vital sign variables and ECG will be summarized descriptively for observed values, by grade and by change from Baseline by cycle. All AEs and lab parameters will be listed.

Interim Analyses

An interim analysis may be performed by the sponsor after 16 subjects in Stage 1 have completed at least 2 tumor assessments (eg, Week 16 tumor assessments), unless discontinued due to disease progression, death or toxicity. If one or no responders are observed in the interim analysis, the study will be stopped early for futility and subjects on study at that time will continue treatment under the discretion of the investigator. If 2 or more responders are confirmed before the planned interim analysis and the safety profiles of both drugs are acceptable, the study will continue to Stage 2 and a formal interim analysis may be waived. There will be no enrollment gap for the interim analysis

Sample Size Rationale

Approximately 31 subjects, including 16 in the first stage, will be enrolled in the study. The actual one-sided type I error is 0.0319 and the power is 0.8053 in the proposed Simon's Two-Stage design. At interim analysis, the probabilities of early futility stopping are 0.6299 under H_0: ORR=8% and 0.0635 under H_a: ORR≥25%, respectively.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ADL	activities of daily living
ATC	Anatomical Therapeutic Chemical
AKT	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ß-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BCRP	breast cancer resistance protein
BOR	best overall response
BP	blood pressure
CA	Competent Authority
CBR	clinical benefit rate
C1D1	Cycle 1 Day 1
C1D15	Cycle 1 Day 15
ccRCC	clear cell renal cell carcinoma
CDC	collecting duct carcinoma
CI	confidence interval
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA

Abbreviation	Term
CV	curriculum vitae
CYP	cytochrome P450
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
EAS	Evaluable Analysis Set
EBRT	external beam radiotherapy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EAS	Evaluable Analysis Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FKBP-12	FK506 binding protein-12
GCP	Good Clinical Practice
ß-hCG	beta-human chorionic gonadotropin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL-C	high density lipoprotein-C
HER2	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HPLC	high pressure liquid chromatography
HR	heart rate
HUVEC	human umbilical vein endothelial cell
ICF	informed consent form

Abbreviation	Term
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IIR	independent imaging review
IND	investigational new drug
IRB	Institutional Review Board
KIT	C-kit receptor CD 117
LD	longest diameter
LDL-C	low-density lipoprotein cholesterol
LLT	lower level terms
LMWH	Low-molecular-weight heparin
MDP	methylene diphosphonate
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mTOR	Mammalian target of rapamycin
nccRCC	non clear cell renal cell carcinoma
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NSAID	nonsteroidal anti-inflammatory
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PDGFR	platelet-derived growth factor receptor
PE	physical examination
PET	proton-emission tomography
PFS	progression-free survival
PG	pharmacogenomics
PgP	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic

Abbreviation	Term
P13K	phosphoinositide 3-kinase
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
PVC	polyvinyl chloride
QD	once a day
RBC	red blood cell
RCC	renal cell carcinoma
RET	rearranged during transfection
RF	radiofrequency
RECIST	Response Evaluation Criteria in Solid Tumors
RMC	renal medullary carcinoma
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
S6K1	S6 ribosomal protein kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TC	total cholesterol
TEAE	Treatment Emergent Adverse Even
TG	triglycerides
TNM	tumor-node-metastasis
TSH	thyroid stimulation hormone
T4	thyroxine
ULN	upper limit of normal
US 21 CFR	Title 21 of the United States Code of Federal Regulations
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary
^{99}m-Tc	^{99}m-technetium

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council on Harmonisation (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. Upon completion of the study, the investigator or sponsor will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject or guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site. Subjects will be asked to either sign a separate ICF for pharmacokinetic (PK) assessments or provide consent for PK assessments within the main ICF. For biomarker assessments, subjects will be asked to either sign a separate ICF or provide consent within the main ICF (see Section 9.5.1.3.2). Subjects may also be asked to either sign a separate ICF or provide consent within the main ICF to allow the sponsor to request scans of their tumor assessments for central review.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's

willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 8 investigational sites in the United States.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor are listed in the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 Indication

This is a single-arm, multicenter, Phase 2 study of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic non clear cell renal cell carcinoma (nccRCC) who have not received any chemotherapy for advanced disease.

Renal cell carcinoma (RCC), which originates within the renal cortex from the proximal renal tubular epithelium, is the most common kidney cancer, constituting 80 to 85 percent of primary renal neoplasms (Wahal and Mardi, 2014). An estimated 62,700 new cases of kidney (renal) cancer are expected to be diagnosed and an estimated 14,240 deaths from kidney cancer are expected to occur in 2016 (American Cancer Society, 2016).

RCC is broadly classified as clear cell renal cell carcinoma (ccRCC), which constitutes approximately 75 to 80% of RCC and non clear cell renal carcinoma (nccRCC), which constitute approximately 20% to 25% of the total RCC disease burden. Non clear cell renal carcinoma (nccRCC) is a group of heterogeneous diseases, which are grouped together due to their low incidence rather than due to their underlying pathology or clinical outcomes. The most common type of nccRCC is papillary and constitutes approximately 15% of kidney cancers, followed by chromophobe (5%), collecting duct (1%), and translocation associated RCC (<1%). The objective response rate (ORR) for nccRCC with targeted agents is approximately 8.3% with a median overall survival (OS) approximately 11.6 months (Hudes, et al., 2007).

Non clear cell RCC has shown an increased expression of vascular endothelial growth factor (VEGF) and its receptors (Ljungberg, et al., 2006). Also, the pathway of mammalian target of rapamycin (mTOR), a key regulatory kinase, has been shown to be deregulated in a significant number of patients with nccRCC (Davis, et al., 2014).

7.1.1 Current Therapeutic Options

The current treatment approach for patients with metastatic nccRCC mirror that of clear cell RCC due to lack of randomized data and consists of sequential administration of single agent therapies that target either the VEGF/VEGF receptor (VEGFR) or mTOR pathways (Escudier, et al., 2014).

Hence, the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines list clinical trials as the preferred option. Temsirolimus is the only Food and Drug Administration (FDA) approved agent (Hudes, et al., 2007). Other agents that are available include sorafenib, sunitinib, pazopanib, axitinib, everolimus, bevacizumab, and erlotinib. Of these, everolimus inhibits mTOR, resulting in downstream inhibition of protein synthesis and cell proliferation (AFINITOR® US Package Insert). Therefore, there remains a significant unmet medical need for more effective treatment options, including possible combination therapies, with a manageable safety profile in patients with advanced RCC.

7.1.2 Lenvatinib

Lenvatinib (LENVIMA®) is a kinase inhibitor that was approved by the US FDA on 13 Feb 2015 and by the European Medicines Agency (EMA) on 28 May 2015, and indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (LENVIMA® US Package Insert/EU SmPC).

7.1.2.1 Mechanism of Action

Lenvatinib is an oral, multiple receptor tyrosine kinase inhibitor (TKI). By inhibiting the kinase activities of various receptors (eg, VEGFR 1-3, fibroblast growth factor receptor [FGFR] 1-4, platelet-derived growth factor receptor [PDGFR] alpha, c-kit receptor CD117 [KIT] and Rearranged during Transfection [RET] protein), lenvatinib impedes pathogenic angiogenesis (development of new blood vessels), tumor growth, and cancer progression (LENVIMA® US Package Insert/EU SmPC).

7.1.3 Everolimus

Everolimus (AFINITOR®) is an inhibitor of mTOR that is indicated for the treatment of adult patients with advanced RCC after failure of treatment with sunitinib or sorafenib (AFINITOR® US Package Insert). It is also indicated for other conditions including: advanced hormone receptor-positive, human epidermal growth factor receptor (HER2)-negative breast cancer; advanced neuroendocrine tumors of pancreatic origin; renal angiomyolipoma with tuberous sclerosis complex; and subependymal giant cell astrocytoma with tuberous sclerosis complex.

7.1.3.1 Mechanism of Action

The mTOR, a serine-threonine kinase, acts as a signal transducing protein in the phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT)/ mTOR pathway, which is known to be involved in numerous human cancers. mTOR regulates protein synthesis, cellular metabolic state, cell proliferation, cell survival and also has some control over the angiogenic pathway through the hypoxia-inducible factor 1 (HIF1α) and VEGF and is linked to endothelial proliferation. Inhibition of the mTOR signaling pathway interferes with protein translation and synthesis by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis.

Everolimus is an mTOR inhibitor. Everolimus binds the intracellular protein FK506 binding protein-12 (FKBP-12), forming a complex which then inhibits mTOR complex-1 (mTORC1) activity. Everolimus reduces levels of VEGF and is a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumors in vitro and in vivo.

7.1.4 Preclinical and Clinical Experience with the Combination of Lenvatinib and Everolimus

7.1.4.1 Preclinical Experience with the Combination of Lenvatinib and Everolimus

Angiogenesis has been identified as a key factor in the development of RCC. A major component of the angiogenic process in RCC is VEGF (Posadas, et al., 2013). An alternative pathway is mediated by mTOR, which is downstream of phosphoinositide 3-kinase and protein kinase B and is regulated by the phosphatase and tensin homolog tumor suppressor gene. Inhibition of the mTOR pathway can inhibit both angiogenesis and tumor cell proliferation (Faivre, et al., 2006). It is hypothesized that combinations of antiangiogenic agents with mTOR inhibitors may overcome the resistance that develops with single agent therapy. With this combination, blockade could take place at two levels of the pathways activated in RCC (at hypoxia-inducible factor and at VEGF) and this may overcome an aspect of resistance that may develop through feedback mechanisms.

Lenvatinib is a potent multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2, VEGFR3) in addition to other proangiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor (FGF) receptors FGFR1-4, PDGF receptor α, KIT, and RET. Lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in human umbilical vein endothelial cell (HUVEC) models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer drugs.

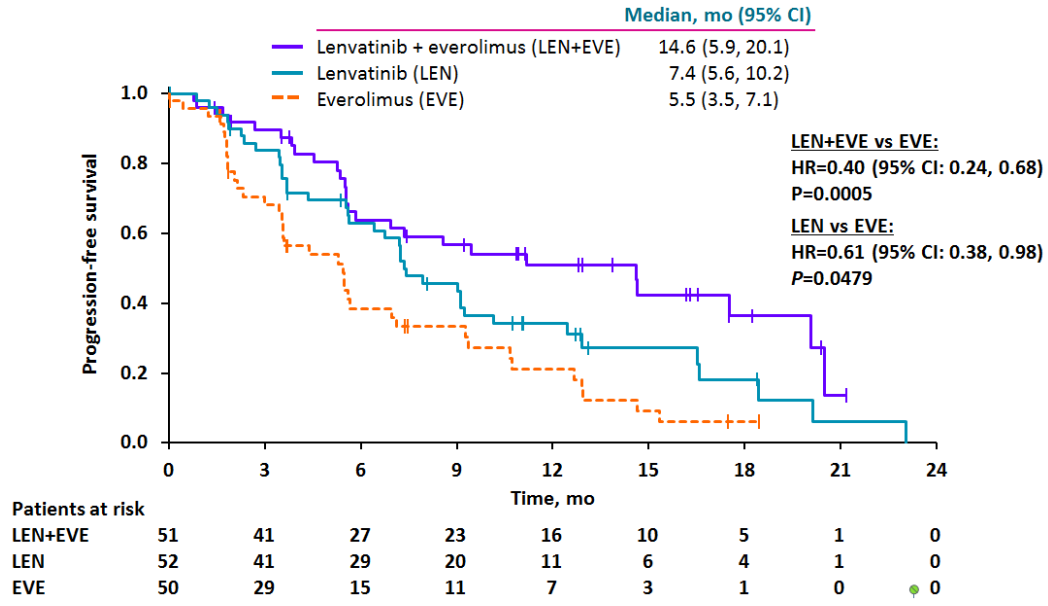
In preclinical models (A498 and Caki-1), the lenvatinib plus everolimus combination demonstrated superior antiangiogenesis as well as antitumor activity compared to each single agent alone (data on file). The mechanism of action of the combination of lenvatinib and everolimus was further investigated in cell-based nonclinical models, and it is hypothesized that the dual inhibition of the VEGF- and FGF-driven mitogen-activated protein kinase (MAPK) and mTOR pathways by the combination of lenvatinib plus everolimus in endothelial cells may contribute to the enhanced antiangiogenic activity of the combination treatment. In addition, the dual targeting of the mTOR-S6K (ribosomal s6 kinase)-S6 pathway by the lenvatinib plus everolimus combination may contribute towards the superior antitumor activity of the combination (data on file).

7.1.4.2 Clinical Experience with Combination Lenvatinib Plus Everolimus Treatment in Renal Cell Carcinoma

The safety and efficacy of lenvatinib and everolimus combination treatment was investigated in the randomized, controlled, open-label study, E7080-G000-205 (hereafter referred to as "Study 205") in subjects with unresectable, advanced or metastatic RCC. Study 205 consisted of a Phase 1b portion and a Phase 2 portion (Motzer, et al., 2015). The recommended Phase 2 dose (RP2D) for the lenvatinib-everolimus combination was lenvatinib 18 mg plus everolimus 5 mg administered daily.

The Phase 2 portion of Study 205 enrolled 153 patients with advanced or metastatic, clear-cell, renal cell carcinoma who had a history of receiving one prior VEGF agent. A total of 153 patients were randomized in a 1:1:1 ratio to receive treatment with lenvatinib plus everolimus, lenvatinib (24 mg once daily [QD]), or everolimus (10 mg QD).

The combination significantly prolonged progression-free survival (PFS) compared with either single agent as shown in the Kaplan-Meier (KM) curve below (Figure 1). In addition, an objective response was achieved by 43% of subjects treated with the combination compared with 6% for single agent everolimus ($p<0.0001$) and 27% for single agent lenvatinib ($p=0.10$).



Source: Study 205 CSR, Figure 4.

Figure 1 Progression-Free Survival of Lenvatinib + Everolimus Versus Single Agent

The safety profile for lenvatinib plus everolimus was consistent with the known toxic effects of each individual agent, with no unexpected treatment-emergent adverse events (TEAEs) observed. The most common TEAEs of any grade in the lenvatinib plus everolimus arm were

diarrhea and fatigue or asthenia. Grade 3 and 4 events occurred in fewer patients allocated single agent everolimus (25 [50%]) compared with those assigned lenvatinib alone (41 [79%]) or lenvatinib plus everolimus (36 [71%]). The most common Grade 3 or 4 TEAE in patients allocated lenvatinib plus everolimus was diarrhea (10 [20%]), in those assigned single agent lenvatinib it was proteinuria (10 [19%]), and in those assigned single agent everolimus it was anemia (6 [12%]). Two deaths were deemed related to study drug, 1 cerebral hemorrhage in the lenvatinib plus everolimus group and 1 myocardial infarction with single agent lenvatinib (Motzer, et al., 2015).

7.2 Study Rationale

Clinical evaluation of lenvatinib in combination with everolimus in subjects who have not received any chemotherapy for advanced disease is warranted based on the following:

- The currently available first-line therapies for RCC are unsatisfactory. These treatments do not induce durable tumor responses and virtually all patients experience progression of disease requiring initiation of another therapy.
- the importance of VEGF, FGF, and mTOR signaling in RCC
- the clinical experience with lenvatinib in metastatic clear cell RCC
- The lack of availability of data to demonstrate that combination therapy in treatment of metastatic nccRCC provides significant advantage over single agent therapy.

It is hypothesized that combinations of targeted agents may overcome the resistance to treatments with single agent therapy. By using an mTOR inhibitor (everolimus) in combination with a VEGFR inhibitor (lenvatinib), blockade could take place at two levels of the pathways activated in RCC and this may overcome an aspect of resistance that may develop through feedback mechanisms.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to evaluate ORR, as assessed by the investigator, of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic nccRCC who have not received any chemotherapy for advanced disease.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess safety and tolerability of lenvatinib in combination with everolimus
- To evaluate PFS as assessed by the investigator

- To evaluate OS
- To assess the PK profiles of lenvatinib and everolimus during combination therapy in subjects with nccRCC

8.3 Exploratory Objectives

The exploratory objectives of the study are:

- To explore ORR as assessed by independent imaging review (IIR)
- To explore PFS as assessed by IIR
- To explore clinical benefit rate (CBR) as assessed by the investigator and by IIR
- To explore disease control rate (DCR) as assessed by the investigator and by IIR
- To explore duration of response (DOR) as assessed by the investigator and by IIR
- To identify and explore tumor and blood biomarkers that correlate with clinical outcomes, including efficacy
- To explore the relationship of population PK derived exposure parameters to biomarker, safety, and efficacy data using a model-based approach

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E7080-M001-221 is a single-arm, multicenter, Phase 2 study of lenvatinib in combination with everolimus (lenvatinib 18 mg/day + everolimus 5 mg/day) in subjects with unresectable advanced or metastatic nccRCC who have not received any chemotherapy for advanced disease. A Simon's Two-Stage Design will be implemented in approximately 31 enrolled subjects. Sixteen subjects will be enrolled in Stage 1. If there are at least 2 responders as assessed by ORR, the study will proceed to Stage 2, in which 15 more subjects may be enrolled. Otherwise, the study will stop early for futility. In the final analysis of 31 subjects, at least 6 responders are required to show a statistically significant improvement of ORR over historical control in the same patient population.

This study consists of three Phases: a Pretreatment Phase (Screening and Baseline Periods), a Treatment Phase (starting Cycle 1, Day 1), and a Posttreatment Phase (End of Treatment Visit and survival Follow-up).

9.1.1 Pretreatment Phase

The Pretreatment Phase will last no longer than 21 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to treatment.

9.1.1.1 Screening Period

Screening will occur between Day –21 and Day –2. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

Subjects must have a histologically-confirmed diagnosis of nccRCC.

The Screening Disposition case report form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.2 Baseline Period

The purpose of the Baseline Period is to establish disease characteristics prior to starting treatment, and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Results of baseline assessments must be obtained and reviewed by the investigator prior to the first dose of study drug, ie, Cycle 1 Day 1 (C1D1), to confirm eligibility. Baseline assessments will be performed on Day -1 or on C1D1 prior to treatment.

Subjects who complete the Baseline Period and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will begin the Treatment Phase.

9.1.2 Treatment Phase

The Treatment Phase will begin at the time of study drug administration on C1D1 and continue in 28-day (4-week) cycles until completion of the off-treatment assessments (within 30 days after the last study drug administration). Lenvatinib 18 mg/day and everolimus 5 mg/day will be administered orally. Subjects will undergo safety and efficacy assessments. Toxicity will be managed by treatment interruption, dose reduction and/or treatment discontinuation. Subjects who discontinue one of the study drugs due to its toxicities may continue to receive the other study drug as long as they demonstrate clinical benefit. Subjects will discontinue both study drugs at the time of confirmed disease progression, development of unacceptable toxicity, withdrawal of consent, or study termination by the sponsor.

9.1.3 Posttreatment Phase

The Posttreatment Phase will start at the End of Treatment Visit and will continue as long as the subject is alive or until the study subject withdraws consent. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessment every 8 weeks ± 1 week until documentation of disease progression or start of another anticancer therapy. Follow-up assessment for survival will be performed every 12 weeks ±1 week.

9.2 Discussion of Study Design, Including Choice of Control Groups

This is a single-arm, multicenter, Phase 2 study of lenvatinib in combination with everolimus (lenvatinib 18 mg/day + everolimus 5 mg/day) in subjects with unresectable advanced or metastatic nccRCC who have not received any chemotherapy for advanced disease. The current treatment approach for patients with metastatic nccRCC mirror that of clear cell RCC due to lack of randomized data and consists of sequential administration of single agent therapies that target either the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) or mammalian target of rapamycin (mTOR) pathways. As discussed in Section 7.1.4, combining everolimus (an mTOR inhibitor) with lenvatinib (a VEGFR inhibitor) could block the pathways activated in RCC at 2 levels and may overcome an aspect of resistance, which develops with single agent therapy. The combination of lenvatinib and everolimus is chosen based on robust results from Study 205.

The current study is designed to provide efficacy and safety data for lenvatinib in combination with everolimus in this patient population. A recently reported Phase 1b/2 study in RCC showed a response rate of 43.1% and median PFS of 14.6 months (95% CI 5.9-20.1). The primary objective of the study is to evaluate ORR. The efficacy and safety parameters being evaluated are commonly used in oncology trials.

9.3 Selection of Study Population

Approximately 31 subjects will be enrolled at approximately 8 sites in regions that include the United States. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Males or females age ≥ 18 years at the time of informed consent form.

2. Histologically confirmed nccRCC who have not received any chemotherapy for advanced disease. Subjects must have one of the following subtypes of nccRCC: papillary, chromophobe, collecting duct carcinoma (CDC), renal medullary carcinoma (RMC), or unclassified.

3. Radiologically measurable disease meeting the following criteria:

a. At least 1 lesion of ≥ 10 mm in the longest diameter for a nonlymph node or ≥ 15 mm in the short axis diameter for a lymph node which is serially measurable according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (Appendix 1) using computerized tomography (CT) or magnetic resonance imaging (MRI).

b. Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of subsequent progressive disease (PD) (substantial size increase of ≥20%) to be deemed a target lesion.

4. Eastern Cooperative Oncology Group (ECOG) (Appendix 2) performance status of 0 to 1.

5. Blood pressure (BP) ≤ 140/90 mmHg at Screening with or without antihypertensive medications and no change in antihypertensive medications within 1 week prior to C1D1.

6. Adequate renal function as evidenced by calculated creatinine clearance ≥ 30 mL/min according to the Cockcroft and Gault formula (Appendix 3).

7. Adequate bone marrow function:

   a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L and

   b. Hemoglobin ≥ 10.0 g/dL (can be corrected by growth factor or transfusion prior to first dose of study drug) and

   c. Platelet count ≥ 100×10^9/L

8. Adequate liver function:

   a. Bilirubin ≤ 1.5 × upper limit of normal (ULN) except for unconjugated hyperbilirubinemia or Gilbert's syndrome

   b. Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if subject has liver metastases). If ALP is > 3 × ULN (in the absence of liver metastases) or > 5 × ULN (in the presence of liver metastases) AND subjects are also known to have bone metastases, the liver-specific ALP must be separated from the total and used to assess the liver function instead of the total ALP.

9. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Predominant clear cell RCC.
2. Prior anticancer chemotherapy or targeted therapy for advanced nccRCC.
3. Prior exposure to lenvatinib or mTOR inhibitor.
4. Known intolerance to lenvatinib, everolimus (or other rapamycin derivatives), or any of the excipients.
5. Major surgery performed within 3 weeks prior to the first dose of study drugs or scheduled for major surgery during the study.
6. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib or everolimus.
7. Subjects having > 1 + proteinuria on urine dipstick testing will undergo 24 hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥ 1 g/24 hours will be ineligible.
8. Fasting total cholesterol >300 mg/dL (or >7.75 mmol/L) or fasting triglycerides level >2.5 × ULN. NOTE: these subjects can be included after initiation or adjustment of lipid-lowering medication.
9. Uncontrolled diabetes as defined by fasting glucose > 1.5 times the ULN. NOTE: In case this threshold is exceeded, these subjects can only be included after initiation or adjustment of glucose-lowering medication.
10. Known history of, or any evidence of, interstitial lung disease or active noninfectious pneumonitis.
11. Significant cardiovascular impairment: History of (a) congestive heart failure greater than New York Heart association (NYHA) (Appendix 4) Class II, (b) unstable angina, (c) myocardial infarction (d) stroke, or (e) cardiac arrhythmia associated with hemodynamic instability within 6 months of the first dose of study drugs.
12. Prolongation of QTcF interval to >480 msec.
13. Known history of human immunodeficiency virus (HIV) positive.
14. Known active hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (eg, hepatitis C virus [HCV] RNA detected).
15. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.
16. Subjects with central nervous system (CNS) (eg, brain or leptomeningeal) metastases.
17. Other active malignancy (except definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within past 24 months.
18. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of

ß-hCG or hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

19. Females of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period or for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexually active during the study period or for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study or for 28 days after study drug discontinuation.
    - Are using oral hormonal contraceptives and who do not agree to add a barrier method.
    - (NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]).
20. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 28 days after study drug discontinuation). No sperm donation is allowed during the study period or for 28 days after study drug discontinuation.
21. Evidence of clinically significant disease (eg, cardiovascular, respiratory, gastrointestinal, renal, or infectious disease) that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments.
22. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
23. Active and current use of illegal recreational drugs.
24. Currently enrolled in another interventional clinical study or used any investigational drug or device within the past 28 days preceding informed consent.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason.

The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Follow-Up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. The Subject Discontinuation From Treatment Phase CRF page will be completed indicating the reason for discontinuation. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing CRF page.

During the Follow-Up Period, subjects who have discontinued study treatment before disease progression will continue to undergo tumor assessment every 8 weeks ±1 week until disease progression is documented or another anticancer therapy is initiated.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis. Subjects will be followed for survival every 12 weeks ±1 week after the End of Treatment Visit. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.

A subject who discontinues study treatment should be followed for subsequent protocol-specified visits and procedures. If a subject discontinues study drug(s) but remains in the study, the set of End of Treatment procedures will be administered, and protocol-specified information will be collected. The reason for discontinuation from study drug(s) should be collected on the Subject Disposition From Treatment Phase CRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing CRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatments

The study drugs under evaluation are lenvatinib in combination with everolimus.

9.4.1 Treatments Administered

Lenvatinib will be provided as 4-mg and 10-mg capsules and everolimus will be provided as 5 mg tablets.

Initial doses of lenvatinib 18 mg/day (one 10-mg capsule and two 4-mg capsules) and everolimus 5 mg/day are to be taken orally in immediate succession once a day (QD), recommended approximately at the same time each morning (consistently either with or without food).

The following treatments will be administered to subjects in this study (Table 1).

Table 1 Treatment Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency	Duration[a]
Lenvatinib	10 mg	Capsule	1 × 10 mg capsule, once a day, recommended at approximately same time each morning	Daily
Lenvatinib	4 mg	Capsule	2 × 4 mg capsule, once a day, recommended at approximately same time each morning	Daily
Everolimus	5 mg	Tablet	1 × 5 mg tablet, once a day, recommended at approximately same time each morning	Daily

a. Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor discontinuation.

9.4.1.1 Criteria for Interruption of Treatment, Dose Reduction, and Resumption of Treatment

If a subject cannot tolerate lenvatinib due to its toxicities, the lenvatinib dose may be reduced, interrupted or discontinued according to the guidelines provided in Table 2 and Table 3. Lenvatinib dose reductions occur in succession based on the previous dose level, ie, one level at a time from 18 mg/day to 14, 10, and 8 mg/day. Any dose reduction below 8 mg/day must be discussed with the sponsor.

If a subject cannot tolerate everolimus due to its toxicities, the everolimus dose may be reduced, interrupted or discontinued. Everolimus dose may be reduced from 5 mg/day to 5 mg every other day.

Dose adjustments for both study drugs will be made according to the guidelines provided in Table 3 for management of intolerable toxicities. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required. Once the dose has been reduced, it cannot be increased at a later date.

Table 2 Dose Reduction Recommendations for Lenvatinib in Combination With Everolimus

Initial Lenvatinib Dose (mg, QD)	Adjusted Dose To Be Administered (mg, QD)			
	Reduction 1	Reduction 2	Reduction 3	Reduction 4
18	14	10	8	a

QD = once daily.
a: Consult Sponsor for further dose reduction recommendations.

Refer to appropriate section for management of hypertension (Section 9.4.1.1.1), proteinuria (Section 9.4.1.1.2), hepatic injury (Section 9.4.1.1.3), thromboembolic events (Section 9.4.1.1.4), posterior reversible encephalopathy syndrome (PRES) (Section 9.4.1.1.5), hypocalcemia (Section 9.4.1.1.6), noninfectious pneumonitis (Section 9.4.1.1.7), infections (Section 9.4.1.1.8), and blood glucose / lipids (Section 9.4.1.1.9) before consulting the table below, as appropriate.

Table 3 Lenvatinib-Everolimus Combination Therapy Dose Reduction and Interruption Instructions[a]

Lenvatinib/Everolimus Treatment-Related Toxicity[b,c] Including Hepatic Injury and Thromboembolic Events	**During Therapy**	**Adjusted Dose**
Grade 1 Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c]		
First occurrence	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1	Dose reduction of lenvatinib (one dose reduction level, see Table 2 above) and, if combination dosing, resume everolimus at the same dose as prior to dose interruption.
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1	Dose reduction of lenvatinib (one dose reduction level, see Table 2 above) and, if combination dosing, resume everolimus at the same dose as prior to dose interruption.
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1	Dose reduction of lenvatinib (one dose reduction level, see Table 2 above) and, if combination dosing, resume everolimus at the same dose as prior to dose interruption.
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1	Discuss with sponsor
Grade 3[d,e]		
First occurrence	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1[f]	Dose reduction of lenvatinib (one dose reduction level, see Table 2 above) and, if combination dosing, resume everolimus at the same dose as prior to dose interruption.
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1 o[f]	Investigator to decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs was required. Dose reduction of lenvatinib (one dose reduction level, see Table 2 above) and/or reduce everolimus to 5 mg every other day.
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and, if combination dosing, interrupt everolimus until resolved to tolerable Grade 2 or Grade 0-1[f]	Investigator to decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs was required. Dose reduction of lenvatinib (one dose reduction level, see Table 2 above) and/or adjust everolimus as follows: i) if 5 mg daily everolimus at event onset, reduce to 5 mg every other day, or ii) if 5 mg every other day everolimus at

Table 3 Lenvatinib-Everolimus Combination Therapy Dose Reduction and Interruption Instructions[a]

Lenvatinib/Everolimus Treatment-Related Toxicity[b,c] Including Hepatic Injury and Thromboembolic Events	During Therapy	Adjusted Dose
		event onset, discontinue.
Fourth occurrence	Interrupt lenvatinib and everolimus	Discuss with sponsor
Grade 4[g]: Discontinue lenvatinib and everolimus		

Note: For grading see Common Terminology Criteria (CTC) for Adverse Events (AE) version 4.03. Collect all CTC grades of AEs, decreasing and increasing grade.

a: A delay of lenvatinib/ everolimus treatment for more than 28 days (due to lenvatinib/ everolimus-related toxicities) requires a discussion with the sponsor before treatment may be resumed.

b: Excluding alopecia. Drug interruption and dose reduction may be initiated for intolerable Grade 2 and Grade 3 related symptoms such as anemia, lymphocytopenia, asymptomatic neutropenia if there are no other treatment options available and the investigator considers that dose interruption or reduction of study medication is the only remaining alternative. Optimal medical management for nausea, vomiting, and/or diarrhea have to be initiated prior to any lenvatinib/ everolimus interruption or dose reduction.

c: Applicable only to Grade 2 toxicities judged by the subject and physician to be intolerable. If Grade 2 toxicity is determined to be intolerable, the dose of study drug will be reduced with or without dose interruption. Interruption for Grade 3 toxicities is mandatory.

d: Obese subjects with weight loss requiring dose interruption and reduction do not need to return to baseline or Grade 1 weight loss to restart lenvatinib. Based on the judgment of the investigator, subjects may be restarted at the lower dose of lenvatinib once the weight has been stable for at least 1 week. Normal body mass index (BMI) should be used as the new baseline for future dose reductions.

e: Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator (eg, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (γ-GTP) values < 10 × upper limit of normal (ULN), and Na).

f: For hematology toxicities, restart treatment after toxicity resolves to Grade 2.

g: Excluding laboratory abnormalities judged to be nonlife-threatening, in which case have to be managed as Grade 3.

9.4.1.1.1 MANAGEMENT OF HYPERTENSION

Lenvatinib-everolimus combination therapy should be withheld in any instances where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP significantly ≥ 160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). Once the BP is controlled, lenvatinib-everolimus combination therapy should be resumed as described below.

The following guidelines should be followed for the management of systolic BP ≥ 140 mmHg up to < 160 mmHg or diastolic BP ≥ 90 mmHg up to < 100 mmHg confirmed on repeat measurements after an hour, for subjects receiving lenvatinib-everolimus combination therapy:

- Continue lenvatinib-everolimus combination therapy and institute antihypertensive therapy for subjects not already receiving this.

- For subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensive should be added.

The following guidelines should be followed for the management of systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg confirmed on repeat measurements after an hour, for subjects receiving lenvatinib-everolimus combination therapy:

- If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib-everolimus combination therapy administration should be interrupted and restarted when BP ≤ 150/95 mmHg at a dose of: one level of dose reduction (ie, 14-mg once daily) per Table 3 of lenvatinib. Resume everolimus at the same dose as prior to dose interruption.
  - If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the first reduced dose (ie, 14-mg once daily) despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib-everolimus combination therapy administration should be interrupted and restarted when BP ≤ 150/95 mmHg at a dose of : one level of dose reduction (ie, 10 mg once daily) per Table 2 and Table 3 of lenvatinib. Resume everolimus at the same dose as prior to dose interruption.
  - If systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg recurs on the next reduced dose (ie, 10 mg once daily) despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib-everolimus combination therapy administration should be interrupted and restarted when BP ≤ 150/95 mmHg at a dose of: one level of dose reduction (ie, 8 mg once daily) per Table 2 and Table 3 of lenvatinib. Resume everolimus at the same dose as prior to dose interruption.
  - Additional dose reduction should be discussed with the sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management.
- Discontinue lenvatinib-everolimus combination therapy.

9.4.1.1.2 MANAGEMENT OF PROTEINURIA

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Visits and Procedures/Assessments. Guidelines for assessment and management of proteinuria are summarized as follows for subjects receiving lenvatinib-everolimus combination therapy:

- Initial episode of proteinuria: if proteinuria ≥ 2+ is detected on urine dipstick testing, lenvatinib-everolimus combination therapy will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Grading according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03) (Appendix 5) will be based on the 24-hour urinary protein result. Management of lenvatinib-everolimus

combination therapy will be based on the grade of proteinuria according to the Dose Reduction and Interruption Instructions (Table 3). Where lenvatinib-everolimus combination therapy is interrupted and restarted, everolimus should resume at the same dose as prior to dose interruption and not as instructed in Table 3.

- Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+, trace, or negative for 3 consecutive months. Any subsequent increases in the level of proteinuria ≥2+ on urine dipstick testing must be confirmed with a 24-hour urinary protein test, which will be assessed and graded, and continued management of lenvatinib-everolimus combination therapy administration will be based on the Dose Reduction and Interruption Instructions (Table 3). Where lenvatinib-everolimus combination therapy is interrupted and restarted, everolimus should resume at the same dose as prior to dose interruption and not as instructed in Table 3. If a new event of proteinuria ≥ 2+ occurs, the subject must resume urine dipstick testing for evaluation of proteinuria every 2 weeks until results are 1+, trace, or negative for 3 consecutive months.

9.4.1.1.3 Management of Hepatotoxicity

Regular monitoring of liver function tests (ALT, AST, and bilirubin levels) should be conducted as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in the Dose Reduction and Interruption Instructions (Table 3) should be followed. Appropriate supportive care should be provided along with close monitoring. If hepatic failure occurs the lenvatinib-everolimus combination therapy must be discontinued.

9.4.1.1.4 Management of Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, signs of deep vein thrombosis (DVT) including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Dose Reduction and Interruption Instructions (Table 3) should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, lenvatinib-everolimus combination therapy must be discontinued.

9.4.1.1.5 Management of Posterior Reversible Encephalopathy Syndrome

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of lenvatinib-treated subjects. PRES is a neurological disorder, which can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES.

Appropriate measures should be taken to control BP. If subject develops PRES, contact study sponsor.

9.4.1.1.6 MANAGEMENT OF HYPOCALCEMIA

Serum calcium should be monitored at least monthly and replace calcium as necessary during lenvatinib treatment. Interrupt and adjust lenvatinib dosing as necessary depending on severity, presence of electrocardiogram (ECG) changes, and persistence of hypocalcemia.

9.4.1.1.7 MANAGEMENT OF NONINFECTIOUS PNEUMONITIS

Noninfectious pneumonitis is a recognized class effect of rapamycin derivatives, including everolimus. Noninfectious pneumonitis (including interstitial lung disease) was described in 12% of subjects taking everolimus. Some cases were severe and on rare occasions, a fatal outcome was observed. Investigators should therefore consider a diagnosis of noninfectious pneumonitis in subjects presenting with nonspecific respiratory signs and symptoms and in whom infectious, neoplastic and other nonmedicinal causes have been excluded by means of appropriate investigations.

Guidelines for assessment and management of noninfectious pneumonitis are summarized as follows for subjects receiving lenvatinib-everolimus combination therapy:

- Subjects who develop radiological changes suggestive of noninfectious pneumonitis and have few or no symptoms (CTCAE Grade 1) may continue lenvatinib-everolimus combination therapy without dose adjustments.
- If symptoms are CTCAE Grade 2:
    - Starting dose of lenvatinib combination therapy with 5 mg daily everolimus: combination therapy should be interrupted and the use of corticosteroids may be indicated until symptoms abate (resolved to CTCAE Grade 0-1 or baseline) and may be restarted with 5 mg everolimus daily in combination with lenvatinib (ie, lenvatinib reinitiated at the same dose as prior to dose interruption) administered daily. Discontinue everolimus if failure to recover within 4 weeks of reinitiating treatment, and continue lenvatinib as a single agent therapy depending on individual clinical circumstance.
    - If Grade 2 noninfectious pneumonitis recurs despite optimal management, then lenvatinib-everolimus combination therapy administration should be interrupted and the use of corticosteroids may be indicated until symptoms abate (resolved to CTCAE Grade 0-1 or baseline). Lenvatinib may be reinitiated as a single agent therapy depending on individual clinical circumstances.
- If symptoms are CTCAE Grade 3:
    - Starting dose of lenvatinib combination therapy with 5 mg daily everolimus: combination therapy should be interrupted and the use of corticosteroids may be indicated until clinical symptoms resolve. Lenvatinib may be reinitiated as single agent therapy depending on the individual clinical circumstances.
- If symptoms are CTCAE Grade 4:
    - Study medications should be discontinued.

9.4.1.1.8 MANAGEMENT OF INFECTIONS

Everolimus has immunosuppressive properties and may predispose subjects to infections. Therefore, monitor for signs and symptoms of infection and treat promptly. Dose alterations of everolimus (either as single agent or in lenvatinib-everolimus combination therapy) may be required in accordance with prescribing information.

9.4.1.1.9 MANAGEMENT OF BLOOD GLUCOSE AND LIPIDS

Hyperglycemia, hyperlipidemia, and hypertriglyceridemia are recognized class effects of rapamycin derivatives, including everolimus. Glycemic control should be optimized before starting a subject on this study.

Blood glucose will be monitored as specified in the Schedule of Visits and Procedures/Assessments. For subjects with blood glucose > ULN, a fasting (> 6h, water only) blood glucose sample will be obtained. Grading according to CTCAE will be based on the fasting blood glucose result. Insulin and/or oral hypoglycemic agents may have to be introduced (or the dose increased) to control blood glucose levels. The choice of hypoglycemic agent should be individualized to the subjects' clinical circumstances and follow standard medical practice in addition to consideration of avoiding coadministration of everolimus with inhibitors and inducers of cytochrome P450 (CYP)3A4 and/or the multidrug efflux pump P-glycoprotein (PgP).

Dose alterations of everolimus (either as single agent or in lenvatinib-everolimus combination therapy) may be required in accordance with prescribing information. Where lenvatinib-everolimus combination therapy is interrupted, lenvatinib should resume at the same dose as prior to dose interruption.

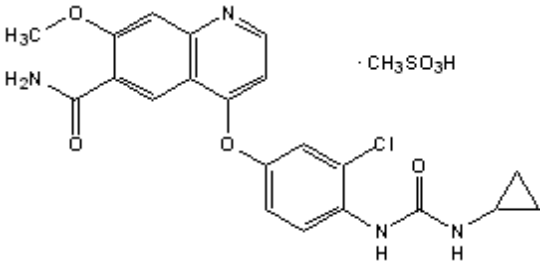
Subjects who are discontinued from one of the study drugs due to intolerance to that drug may continue to receive the other study drug as long as they demonstrate clinical benefit.

9.4.2 Identity of Investigational Products

The sponsor will provide the study drugs as open-label supplies.

9.4.2.1 Chemical Name, Structural Formula of Lenvatinib

- Test drug code: E7080
- Generic name: lenvatinib
- Chemical name: 4-[3-Chloro-4-(N'-cyclopropylureido) phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate
- Molecular formula: $C_{21}H_{19}ClN_4O_4 \bullet CH_3SO_3H$
- Molecular weight: 522.96
- Structural formula:



9.4.2.2 Chemical Name, Structural Formula of Everolimus

- Trade name: Afinitor®
- Test drug code: NA
- Generic name: everolimus
- Chemical name: 40-O-(2-hydroxyethyl)-rapamycin
- Other names: RAD001, Certican, SDZ RAD
- Molecular formula: $C_{53}H_{83}NO_{14}$

9.4.2.3 Comparator Drug

Not applicable.

9.4.2.4 Labeling for Study Drug

Lenvatinib and everolimus will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

The following information will be included in the label (but not limited to):

- Protocol Number
- Name and address of the sponsor
- Pharmaceutical dosage form, route of administration, quantity of dosage units, identifier, and potency
- Lot number/batch number
- Storage conditions, expiration date if necessary
- CAUTION: New Drug-Limited by the United States law to investigational use.

9.4.2.5 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a

calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

Clinical experience with the combination of lenvatinib 18 mg QD plus everolimus 5 mg QD in Study 205 shows that combination therapy results in significant prolongation of PFS compared with lenvatinib and everolimus as single agents in patients with metastatic RCC. The median PFS of 14.6 months for the combination of lenvatinib and everolimus is clinically relevant and longer than the PFS duration for any other agents approved for treatment of RCC. The combination of lenvatinib plus everolimus is associated with acceptable and manageable toxicity, with no overlapping or unexpected treatment-emergent adverse events.

9.4.5 Selection and Timing of Dose for Each Subject

Lenvatinib capsules and everolimus tablets are to be taken orally QD at approximately the same time in the morning without regard to food intake from C1D1 onward. A cycle is considered 28 days. The two drugs should be administered in immediate succession. If a subject misses a dose, it may be taken within the 12 hours following the usual time of the morning dose. If more than 12 hours have elapsed from the time of the usual daily dose, study drugs should be taken the next day at the usual time in the morning. In the event a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose. Subjects should not take a double dose (two doses at the same time) to make up for a forgotten dose.

Lenvatinib capsules should be swallowed whole with water each morning. Caregivers should avoid exposure to the contents of the capsule. Lenvatinib is supplied in high density polyethylene (HDPE) bottles and the capsules should only be removed at the time of the administration because the drug is hygroscopic.

Everolimus tablets should be swallowed whole with a glass of water. The tablet should not be chewed or crushed. Everolimus is supplied in aluminium/polyamide/aluminium/polyvinyl chloride (PVC) blisters. Each tablet should be opened only at the time of administration because the drug is hygroscopic and light-sensitive.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 28 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the study drugs may be continued during the study.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study drugs.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. Granulocyte colony-stimulating factor or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell (RBC) counts. Both systemic and inhalant forms of corticosteroids are permissible.

If the subject is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib for 2 days before the procedure and restart it 2 days after, once there is clear evidence of wound healing and no risk of bleeding, but at least 2 days after the procedure.

- For major procedures: hold lenvatinib for 1 week (5 half-lives) prior to surgery and then restart when there is clear evidence of wound healing and no risk of bleeding, but at least 1 week after the procedure.

If the subject is receiving treatment with everolimus and requires surgery during the study, refer to the AFINITOR® US Package Insert.

If concomitant medication/therapy is administered for an AE, investigators will record that AE on the Adverse Events CRF.

9.4.7.1 Drug-Drug Interactions

No dose adjustment of lenvatinib is recommended when coadministered with CYP3A, PgP, and breast cancer resistance protein (BCRP) inhibitors, and with CYP3A and PgP inducers (LENVIMA® US Package Insert). Similarly, lenvatinib at the proposed dose for clinical use is not expected to inhibit the cytochrome P450-mediated metabolism of other drugs

administered concomitantly (CPMS-E7080-007R-v1, RDMPKA2013-156 REVISION NO. 1).

A population PK analysis also indicated that agents that raise gastric pH (eg, H2-blockers, proton pump inhibitors, antacids) do not have a significant effect on the absorption and bioavailability of lenvatinib (CPMS-E7080-007R-v1).

Everolimus is a substrate of CYP3A4 and also a substrate and moderate inhibitor of PgP. In vitro results indicate that everolimus inhibition of PgP and CYP3A4 is unlikely. However, everolimus may affect the bioavailability of coadministered drugs that are CYP3A4 and/or PgP substrates since inhibition of CYP3A4 and PgP in the gut cannot be excluded.

Drugs metabolized by CYP3A4 or drugs that are inhibitors or inducers of CYP3A4 (including herbal supplements or grapefruit) could affect the metabolism of everolimus.

Please refer to Flockhart DA, 2007 for the most current information regarding inhibitors and inducers of CYP3A4.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If subjects receive additional antitumor therapies during the study, such as radiotherapy, other chemotherapy, or immunotherapy, this will be judged to represent evidence of disease progression, and continuation of study medication should be discussed with the sponsor. Following this discussion, if the joint decision is made to discontinue study treatment, then such subjects will complete all End of Treatment assessments and continue to be followed for survival in the Follow-Up Period.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number

- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted, including any other required country-specific documentation and the Importation License

The investigator and the study staff will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator by the subject and, together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation

procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity (record in accordance with prevailing regulations). Baseline characteristics will include ECOG performance status and NYHA cardiac disease classification (see Appendix 2 and Appendix 4, respectively).

9.5.1.1.1 Medical History and Physical Examinations

Significant medical and surgical history and current medical conditions will be obtained during the Pretreatment Phase (Screen and Baseline).

Physical examinations (comprehensive [including neurological examination] or symptom directed) will be performed as designated in the Schedule of Procedures/Assessments (Table 5). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Subjects must have measurable disease according to RECIST v1.1 (Appendix 1) as defined in Inclusion Criterion #3. Tumor-node-metastasis (TNM) staging at diagnosis should follow the guidelines provided in Appendix 6. Subjects must also fulfill the medical and physical characteristics identified in the inclusion criteria and not otherwise meet any of the exclusion criteria.

9.5.1.2 Efficacy Assessments

The primary endpoint (ORR), secondary endpoint (PFS), and exploratory endpoints (CBR, DCR, and DOR) will be evaluated by the investigator. In addition, ORR, PFS, CBR, DCR and DOR will be assessed by IIR. The OS status will be assessed throughout the study.

9.5.1.2.1 TUMOR ASSESSMENTS

Tumor assessments will be performed using RECIST v1.1. Investigator-determined response assessments are to be performed at the site by appropriately qualified personnel at each time point and recorded on the appropriate CRFs. Copies of all tumor assessment scans will be sent to an imaging core laboratory specified by the sponsor for quality assessment and independent imaging review. Tumor assessments will be carried out following the guidelines provided by the imaging core laboratory. Historical scans performed within the Screening period that do not follow the guidelines completely may be used to demonstrate eligibility, as long as they meet minimum standards as separately defined by the imaging core laboratory.

Tumor assessments including a CT chest and CT or MRI of the abdomen and pelvis, and other areas of known or newly suspected disease should be performed prior to Baseline (between Day –28 to Day -2) and every 8 weeks (within the 8th week) from the date of first dose during the Treatment Phase. The same imaging modality and image-acquisition protocol (including use or nonuse of contrast, oral and IV) should be used consistently across all time points. A brain scan will be performed at Screening, and thereafter if clinically indicated. Bone scans using whole body bone MRI, ^{99}m-technetium (^{99}m-Tc) based bone scans, or ^{18}F sodium fluoride positron-emission tomography (Na-F PET) will be performed during the pretreatment phase to establish a baseline (a historical bone scan performed within 6 weeks before first dose is acceptable), every 24 weeks, and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging.

In subjects with complete response (CR) based on body CT/MRI scans, bone scan and brain scan, assessment will be required at response confirmation. All objective responses must be confirmed at least 28 days following the initial achievement of response. Subjects going off study treatments without disease progression in the Treatment Phase will continue to undergo tumor assessments according to the above schedule until disease progression is documented or another anticancer therapy is initiated.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Sparse PK samples will be collected from all subjects and will be analyzed using the population approach. A total of 12 samples (6 plasma samples for lenvatinib and 6 whole blood samples for everolimus) per subject will be obtained at the following time points: 2 to 8 hours postdose on C1D1, prior to dose on Cycle 1 Day 15 (C1D15), prior to dose and 2 to 8 hours postdose on Day 1 of Cycles 2 and 3. Actual time and date of PK blood collection as well as time of drug administration will be recorded on the appropriate page of the CRF.

Refer to the Laboratory Manual for the total blood volume to be collected along with instructions for processing, shipping and handling of the samples.

Lenvatinib in plasma and everolimus in blood will be quantified using validated high pressure liquid chromatography (HPLC)-tandem mass spectroscopy methods.

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Blood and Tissue Biomarkers

Biomarker discovery and/or validation may be performed to identify blood or tumor biomarkers that may be useful to predict subject response to study drug, evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. In addition, biomarkers identified in other clinical studies of study drug may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

A blood sample for pharmacodynamic and exploratory biomarker analysis will be collected predose on Day -1 or C1D1, on C1D15, and on Day 1 of subsequent cycles (during Treatment Phase), and at the End of Treatment assessment. Blood samples from all consented subjects may undergo analyses including, but not limited to, global proteomic and/or enzyme-linked immunosorbent assay (ELISA)-based analyses or multiplex bead-based immunoassay in an effort to assess pharmacodynamic biomarkers.

Pharmacogenomic (PG) Assessments

Archived, fixed tumor tissue will be collected (if available) from all subjects for potential assessment of mutations and other genetic alterations or genes and/or proteins that may be important in the development and progression of cancer as well as in response to study drug treatment for potential use in diagnostic development. Appropriate technology/methodologies will be used based on the amount of tumor tissue available.

A blood sample for peripheral blood mononuclear cells (PBMC) and plasma isolation will be collected from consented subjects for potential analysis of cell free nucleic acid (cf-nucleic acid) analysis and exploratory immune cell analysis. Cell free nucleic acid isolated from plasma samples may be used to obtain circulating tumor DNA (ctDNA) and explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment. PBMCs may be used for immune cell profiling (eg. tumor infiltrating lymphocytes, T-cell repertoire, and immune cell types).

A blood sample will be collected for pharmacogenomics (PG) analysis (except where prohibited by regional or local laws). Variation in lenvatinib exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA

extracted from tumor material are limited to the tumor and for potential profiling of immune cells.

Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib, cancer and/or for potential diagnostic development.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

9.5.1.4 Safety Assessments

General safety will be assessed by the monitoring and recording of all AEs and serious adverse events (SAEs), regular monitoring of hematology and blood chemistry, regular measurement of vital signs, ECG, and the performance of physical examinations (PE) and other safety assessments in line with local regulations governing a study of this nature.

Progression of nccRCC and signs and symptoms clearly related to the disease progression should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

In case of life-threatening bleeding, the investigator should discuss the case with the Eisai Medical Monitor, in addition to discontinuing lenvatinib per Table 2 for Grade 4 toxicity and treat the subject based on the institution's standard practice. Clinically significant bleeding will be considered as study-specific events and should always be considered as serious important medical events, which will be entered on the adverse event CRF and reported using the procedures for reporting SAEs, even if the study-specific event does not meet other serious criteria.

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE v4.03 grades (for both increasing and decreasing severity) (Appendix 5), and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and performance of physical examinations as detailed in Table 5.

9.5.1.4.1 Adverse Events and Events Associated with Special Situations

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drugs are lenvatinib and everolimus.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product,

whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit and for 28 days after the last dose of study treatment. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose of study treatment.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 28 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to Common Terminology Criteria for Adverse Event (CTCAE v4.03). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event if it does not meet other serious criteria: clinically significant bleeding.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 4. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 5) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Efforts should be made to conduct study visits on the day scheduled. If necessary, study visits may be held up to 3 days sooner or later than the scheduled day that clinical laboratory assessments may be conducted according to (Table 5).

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and ANC
Chemistry	
Electrolytes	Bicarbonate, chloride, magnesium, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Thyroid function tests[a]	TSH and free T4
Pregnancy test	Serum β-hCG (if urine not tested)
Fasting blood tests	Glucose, lipids (total cholesterol, LDL-C, HDL-C, triglycerides)
Other	Albumin, amylase, calcium, lactate dehydrogenase, lipase, phosphorus, total protein, uric acid
Urinalysis	glucose, ketones, pH, protein, RBCs, specific gravity
Pregnancy test	Urine β-hCG (if serum not tested)

ANC= absolute neutrophil count, β hCG = beta-human chorionic gonadotropin, HDL-C= high density lipoprotein-C, LDL-C=low density lipoprotein-C, RBC = red blood cells, T4 = thyroxine, TSH = thyroid stimulating hormone, WBC = white blood cells.

a: Thyroid function will be assessed at the Screening Visit, at Baseline/C1D1, Day 1 of every cycle (starting at C2) throughout the study, and at the End of Treatment Visit.

Clinical laboratory tests during the study will be performed by trained staff at the study sites. Local laboratories will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle. Refer to Table 3 for the management of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.4.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], heart rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 5) by a validated method. Height will be measured at the

Screening Visit only. Blood pressure and heart rate will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person, if feasible. For subjects with an elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥ 90 mmHg), confirmation should be obtained by performing repeat measurements after 1 hour to obtain a mean value.

Subjects with systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until systolic BP has been ≤ 150 mmHg and diastolic BP has been ≤ 95 mmHg for 3 consecutive months. If a new event of systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤ 150 mmHg and diastolic BP has been ≤ 95 mmHg for 3 consecutive months.

9.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 5). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.4.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 5). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.4.7 OTHER SAFETY ASSESSMENTS

Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status will be assessed at the Screening Visit, Baseline/C1D1, Day 1 of each treatment cycle starting at Cycle 2, and at End of Treatment Visits. The table in Appendix 2 will be used to assess performance status.

Pregnancy Test

A serum or urine β-hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A 6-mL

sample of blood will be taken at designated time points as specified in the Schedule of Procedures/Assessments (Table 5).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the study.

Table 5 Schedule of Procedures/Assessments for Study E7080-M001-221

Phase	Pretreatment[a,]		Treatment[b] All cycles are 28 days in duration						Posttreatment[c]	
Period	Screening	Baseline	Cycle 1			Cycle 2		Cycle 3 – Last Cycle	End of Treatment	Follow-Up Period
Day	-21 to -2	-1	Day 1[a]	Day 8	Day 15	Day 1	Day 15	Day 1	Within 30 days of last dose	Every 12 weeks[d]
Visit	1	2	3	4	5	6	7	8, 9, 10, etc.		
Informed consent	X									
Inclusion/Exclusion[e]	X	X								
Demographic data[f]	X									
Archival tumor block or slides[g]	X									
Pharmacogenomic blood sample		X								
Biomarker blood serum/PBMC/plasma sample[h]		X			X	X		X	X	
ECOG[i]	X	X				X		X	X	
TNM staging at diagnosis	X									
Medical/surgical history	X	X								
Vital signs[j,k]	X	X		X	X	X	X	X	X	
Physical examination[l]	X	X			X	X		X	X	
12-Lead ECG[m]	X				X	X		X	X	
Clinical chemistry and hematology[n]	X	X			X	X	X[o]	X	X	
Fasting blood glucose[p]	X	X				X		X	X	

Table 5 Schedule of Procedures/Assessments for Study E7080-M001-221

Phase	**Pretreatment[a,]**		**Treatment[b] All cycles are 28 days in duration**						**Posttreatment[c]**	
Period	**Screening**	**Baseline**	**Cycle 1**			**Cycle 2**		**Cycle 3 – Last Cycle**	**End of Treatment**	**Follow-Up Period**
Day	**-21 to -2**	**-1**	**Day 1[a]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Within 30 days of last dose**	**Every 12 weeks[d]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9, 10, etc.**		
Amylase and Lipase	X	X				X		X	X	
Fasting lipids[q]	X	X						X	X	
TSH and free T4 levels[r]	X	X				X		X	X	
Urine dipstick testing[s]	X	X			X	X	X	X	X	
Pregnancy test[t]	X									
PK[u]			X		X	X		X		
Telephone contact										X[d]
Lenvatinib treatment			Once Daily							
Everolimus treatment			Once Daily							
Tumor assessments: CT/MRI[v]	X		Performed every 8 weeks after C1D1, or sooner if clinically indicated, until documentation of disease progression or beginning another anticancer therapy.							
Bone Scan[w]	X		Every 24 weeks ± 1 week after C1D1, or as clinically indicated. In subjects with CR based on body CT/MRI scans, a bone scan assessment will be required at response confirmation.							
Brain Scan[x]	X		If clinically indicated. In subjects with CR based on body CT/MRI scans, a brain scan will be required at response confirmation.							
Survival		Throughout								
Concomitant medications[y]	Throughout									
AEs/SAEs[z]	Throughout									

Table 5 Schedule of Procedures/Assessments for Study E7080-M001-221

Phase	Pretreatment[a,]		Treatment[b] All cycles are 28 days in duration						Posttreatment[c]	
Period	Screening	Baseline	Cycle 1			Cycle 2		Cycle 3 – Last Cycle	End of Treatment	Follow-Up Period
Day	-21 to -2	-1	Day 1[a]	Day 8	Day 15	Day 1	Day 15	Day 1	Within 30 days of last dose	Every 12 weeks[d]
Visit	1	2	3	4	5	6	7	8, 9, 10, etc.		

AEs = adverse events, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D15 = Cycle 1/Day 15, CR = complete response, CT = computerized tomography, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, h = hour, HR = heart rate, med = medical/medication(s), MRI = magnetic resonance imaging, , PK = pharmacokinetics, PBMC= peripheral blood mononuclear cells, PR = partial response, RR = respiratory rate, SAEs = serious adverse events, T4 = thyroxine, TNM = tumor-mode-metastasis, TSH = thyroid stimulating hormone, Tx = treatment, w/in = within.

a. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit. Baseline assessments can be performed on Day -1 or on C1D1 prior to initiation of lenvatinib and everolimus treatment. Informed consent must be obtained up to 21 days prior to C1D1.
b. Efforts should be made to conduct study visits on the day scheduled (± 3 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified.
c. The Posttreatment Phase will start at the End of Treatment visit and will continue as long as the subject is alive or until the subject withdraws consent or is lost to follow-up. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessment every 8 weeks ± 1 week until documentation of disease progression or start of another anticancer therapy. Follow-up assessment for survival will be performed every 12 weeks ± 1 week.
d. Subjects will be followed for survival every 12 weeks ± 1 week after the End of Treatment Visit. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
e. New York Heart Association (NYHA) cardiac disease classification should be performed at Screening only, if needed.
f. Demographic information includes date of birth (or age), sex, and race/ethnicity.
g. Archived, fixed tumor tissue will be collected (if available) and may be used in the future for potential assessment of genetic biomarkers. The decision to perform other biomarker assessments may be based on the clinical outcome of this study and/or the signals observed in other studies or other information available at that time.
h. Collection of blood samples to obtain serum, peripheral blood mononuclear cells, and/or plasma to be used for cell-free nucleic acid, immune cell, and biomarker studies from subjects. Samples will be obtained predose on Day -1 or C1D1, C1D15, Day 1 of all subsequent cycles, and at the End of Treatment Visit.
i. ECOG will be performed at the Screening and Baseline Visits, on C 2/D1, on Day 1 of every subsequent cycle thereafter, and at the End of Treatment Visit.
j. Assessments will include vital signs (resting BP, HR, RR, and body temperature), weight, and height. Height will be measured at the Screening Visit only. Vital signs will be performed at Screening, Baseline, C1D8, C1D15, C2D1, C2D15, Day 1 of every cycle thereafter, all unscheduled visits, and at the End of Treatment Visit. Elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) should be confirmed by repeat measurements after 1 hour to obtain a mean value.

k. Subjects with systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg must have their BP monitored every 2 weeks (on Day 15 or more frequently as clinically indicated) until systolic BP has been ≤ 150 mmHg and diastolic BP has been ≤ 95 mmHg for 3 consecutive months. If a new event of systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤ 150 mmHg and diastolic BP has been ≤ 95 mmHg for 3 consecutive months.

l. A comprehensive physical examination (including a neurological examination) will be performed at the Screening Visit, on Cycle 1/Day 15, on Day 1 of each subsequent cycle, and at the End of Treatment assessment. A symptom-directed physical examination will be performed on Baseline (Day -1) or on C1D1 prior to treatment, and at any time during the study, as clinically indicated.

m. Single 12-lead ECG. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

n. Clinical chemistry and hematology results must be reviewed prior to administration of lenvatinib and everolimus on C1D1 and all subsequent cycles. Scheduled assessments (Screening Visit, Baseline/C1D1, Cycle 1/Day 15, Day 1 of each subsequent cycle starting with Cycle 2 and at the End of Treatment Visit) may be performed within 72 hours prior to the visit. If there is a clinically relevant hematologic or chemistry toxicity of ≥ Grade 3, additional laboratory tests and AE assessments are required until the toxicity improved to < Grade 3.

o. **On C2D15, only liver function (ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin) should be performed.** Note: liver function should be assessed at the Screening Visit, then every 2 weeks for the first two months (Baseline/C1D1, C1D15, C2D1, and C2D15), and then monthly thereafter (Day 1 of each subsequent cycle) and at the End of Treatment Visit.

p. Assessments of fasting blood glucose are to be performed at the Screening Visit, Baseline/C1D1, monthly thereafter on Day 1 of each subsequent cycle starting at Cycle 2, and at the End of Treatment Visit.

q. Assessment of fasting lipids (including total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [TG]) are to be performed at the Screening Visit, Baseline/C1D1, on Day 1 of every 3rd cycle thereafter (Cycles 4, 7, etc.), and at the End of Treatment Visit.

r. Assessment of TSH and free T4 levels are to be performed at the Screening Visit, Baseline/C1D1, Day 1 of each subsequent cycle starting at Cycle 2, and at the End of Treatment Visit.

s. Urinalysis will be performed at Screening, Baseline, Cycle 1/Day 15, Cycle 2/Day 1, Cycle 2/Day 15, Day 1 of every cycle thereafter, all unscheduled visits, and at the End of Treatment Visit. Urinalysis will include glucose (fasting at Baseline only), ketones, pH, protein, RBCs, and specific gravity. If urine protein ≥ 2+ on urinalysis, lenvatinib will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed every 2 weeks (on Day 1 and Day 15 of each cycle or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. If a new event of proteinuria ≥ 2+ occurs, the subject must resume urine dipstick testing for evaluation of proteinuria every 2 weeks until results are 1+ or negative for 3 consecutive months.

t. A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal and perimenopausal women who have been amenorrheic for less than 12 months) at the Screening Visit. If a negative screening pregnancy test is obtained more than 72 hours before the planned first dose of lenvatinib and everolimus, a separate serum or urine sample must be obtained and tested at the Baseline Visit.

u. Sparse PK samples will be collected from all subjects at the following time points: 2-8 hours postdose on C1D1, prior to dose on C1D15, prior to dose and 2-8 hours postdose on Day 1 of Cycles 2 and 3.

v. **Screening:** Screening tumor assessments using CT of the brain, chest, abdomen and pelvis, and other areas of known or newly suspected disease should be performed between Day –28 to Day -2. Detailed imaging guidelines will be provided by the imaging core laboratory. Scans that were performed within this window but before informed consent may be used if they were acquired consistent with the guidelines provided by the imaging core laboratory.
Treatment Phase: Tumor assessments of the chest/abdomen/pelvis and other areas of known disease at Screening plus any areas of newly suspected disease should be performed every 8 weeks (within the 8th week), or sooner if clinically indicated, until documentation of disease progression and should utilize the same methodology and scan acquisition techniques used at Screening to ensure comparability. All objective responses must be confirmed at least 28 days following the initial achievement of the response. The same methodology and acquisition techniques used at Screening should be used throughout the study to ensure comparability.
Follow-up Period: Subjects who discontinue treatment without disease progression should continue tumor assessments every 8 weeks ± 1 week, until disease progression or beginning another anticancer therapy.

w. Bone scans using whole body bone MRI, ^{99}m-technetium based bone scans, or ^{18}F sodium fluoride positron-emission tomography (Na-F PET) will be performed during the pre-treatment phase to establish a baseline (a historical bone scan performed within 6 weeks before first dose is acceptable), every 24 weeks, and as clinically indicated. Lesions identified on bone scans should be followed with cross-sectional imaging.
x. A brain scan will be performed at Screening and thereafter if clinically indicated. In subjects with CR based on body CT/MRI scans, a brain scan assessment will be required at response confirmation.
y. Concomitant medications will be recorded throughout and for 28 days after last dose of lenvatinib and/or everolimus. All anticancer therapy will be recorded until time of death or termination of survival follow-up.
z. Throughout the study from the signature of Informed Consent. SAE irrespective of relationship to study treatment must be reported as soon as possible but not later than 24 h. AEs will be recorded for 28 days after last dose of lenvatinib and/or everolimus. During treatment interruption due to AEs, repeat AE assessments at least every 7 days (until restarting lenvatinib and/or everolimus administration).

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 5 for a description and timing of each procedure and assessment in the Pretreatment, Treatment, and Posttreatment phases.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of nccRCC.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, radiologic studies, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from when the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for up to 28 days after the subject's last dose of study treatment. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which either the estimated date of conception is before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose.
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol.
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects.

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events, consisting of clinically significant bleeding, should always be considered as serious important medical events and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 5).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the

status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these reasons: AE(s), lost to follow-up, subject choice, (ie, subject chooses to discontinue from the treatment but is willing to participate in the Follow-Up portion of the study), progression of disease, withdrawal of consent (ie, subject no longer wishes to participate in the study and be contacted), pregnancy, sponsor discontinuation of the study, or other. Study disposition information will be collected on the Subject Disposition From Treatment Phase CRF page.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released and a snapshot of the database is obtained and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary efficacy endpoint is ORR based on investigator assessment, defined as the proportion of subjects who have a BOR of CR or PR.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary efficacy endpoints are:

- PFS based on investigator assessment – defined as the time from date of first dose of study drug to date of first documentation of disease progression or death, whichever occurs first.
- OS – defined as the time from the date of first dose of study drug until date of death from any cause.

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints are:

- ORR based on IIR assessment.
- PFS based on IIR assessment.
- CBR is the proportion of subjects who have a BOR of CR or PR or durable SD. Stable disease must be achieved at ≥ 23 weeks after first lenvatinib administration to

be considered durable SD. The CBR will be determined based on both investigator and IIR assessments.

- DCR is the proportion of subjects who have a BOR of CR, PR, or SD. The DCR will be determined based on both investigator and IIR assessments.

- DOR is defined as the time from the date that the criteria are met for CR or PR (whichever is recorded first) to the date that PD is objectively documented or death, whichever occurs first. The DOR will be determined based on both investigator and IIR assessments.

9.7.1.2 Definitions of Analysis Sets

The Full Analysis Set (FAS) includes subjects who received at least 1 dose of the study drugs. This will be the analysis set for all efficacy and safety evaluations.

The Evaluable Analysis Set (EAS, a subset of the Full Analysis Set) includes all subjects who have both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless the subjects are discontinued because of disease progression or toxicity. This will be used for the sensitivity analyses of efficacy.

The PK Analysis Set will include all subjects who received at least one dose of study drug and have evaluable lenvatinib plasma and/or everolimus whole blood concentration data.

The Pharmacodynamic Analysis Set will include all subjects who received at least one dose of study drug and have evaluable pharmacodynamics data.

9.7.1.3 Subject Disposition

The number of subjects enrolled, prematurely discontinued from study treatment (defined as those who discontinued study treatment due to any reason except for progressive disease) and those with major protocol deviations will be counted. The reason for study drug discontinued will be summarized according to the categories in the CRF. The end of study status (alive, death, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the survival follow-ups.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, weight, and vital signs; categorical variables include sex, age group, ECOG performance status, race, and subtypes of nccRCC.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number

(percentage) of subjects who took prior and concomitant medications will be summarized on the FAS by Anatomical Therapeutic Chemical (ATC) class and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 28 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Primary endpoint ORR assessed by investigator review will be analyzed using the Full Analysis Set. Subjects who did not have a tumor assessment for any reason will be considered as nonresponders and included in the denominator when calculating response rate.

In this population, ORR in the historical control is assumed to be 8% (Hudes et al.,2007). The ORR in this study is estimated as 25%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H_0: ORR=8%

H_a: ORR ≥25%

Simon's Two-Stage Design (Simon, 1989) is used in hypothesis testing for the primary endpoints. The interim futility analysis after Stage 1 allows for an early evaluation of efficacy results in order to stop the study early in the case of low anticancer activity. A minimum of 2 responders as assessed by ORR in the Stage 1 subjects (n_1=16) is required in the interim analysis for the study to proceed to Stage 2, in which 15 more subjects may be enrolled. In the final analysis of ORR, a minimum of 6 responders is required in Stages 1 and 2 subjects combined (n=31) to claim the superiority of study treatment over historical controls.

The ORR based on investigator assessment in the final analysis will be calculated and a 2-sided Clopper–Pearson 95% confidence interval (CI) will be constructed.

Table 6 Simon's Two-Stage Design for Interim Futility and Final Analyses of ORR

	Threshold
Interim Analysis	Continue if ≥2 responders when n_1=16
Final Analysis	Reject H_0 if ≥6 responders when n=31

H_0 = null hypothesis, n = sample size for Stages 1 and 2 subjects combined, n1 = sample size for Stage 1 subjects, ORR = objective response rate

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The PFS assessed by the investigator and OS will be analyzed using Kaplan–Meier product-limit estimates. Median PFS and OS and the cumulative probability of PFS at 3, 6, and 12 months and cumulative probability of OS at 6, 12, and 18 months will be presented with two-sided 95% CI if estimable. PFS censoring rules will follow FDA Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

The cumulative PFS and OS will be plotted over time. The median, first, and third quartiles from Kaplan–Meier estimation for PFS and OS will be provided with 95% CI if estimable.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

The ORR based on IIR assessment will be evaluated using the same method described in the primary analysis.

A 2-sided Clopper–Pearson 95% CI will be constructed for CBR and DCR. The DOR and PFS per IIR assessment will be analyzed using time to event methods described above.

9.7.1.6.4 FORMAL ANALYSES OF ORR, PFS, AND OS

A formal analysis will be carried out after all subjects have been enrolled and on study treatment for at least 6 months or have discontinued due to disease progression, death, or toxicity. Since the primary endpoint ORR data are expected to be observed sooner than the secondary endpoints, the timing of the formal analysis is chosen such that the secondary endpoints, PFS and OS, will be adequately described. The primary population for efficacy and safety analyses is the FAS.

9.7.1.6.5 SENSITIVITY ANALYSES

The above efficacy analyses will be conducted in the EAS as sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

A population PK approach will be used to characterize the PK of lenvatinib and everolimus and the final PK model will be used to derive lenvatinib and everolimus exposure parameters to be used in the subsequent pharmacokinetic (PK)/pharmacodynamic analyses. The analyses will be detailed in a separate analysis plan. Concentrations of each analyte will be graphed by time within each nominal collection interval. Average dose at each collection interval will also be displayed.

9.7.1.7.2 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Lenvatinib and everolimus exposure parameters derived from the population PK analysis will be related to biomarker, safety, and efficacy data using a model-based approach. For some

PK/pharmacodynamic analyses, data from this study may be pooled with data from other clinical studies of study drug.

For efficacy, a tumor growth inhibition model based on longitudinal tumor size measurements of target lesions will be included. We plan to explore exposure to both lenvatinib and everolimus exposure and/or selected biomarkers, identified in other studies of study drug, as predictors and/or correlations with tumor burden changes in the tumor growth inhibition model. Other analyses will include logistic regression analysis for ORR_{24W}.

For the exposure-response relationship of safety, data will be analyzed using a longitudinal categorical logistic regression analysis for AEs leading to dosing reduction or interruption.

For the exposure-response relationship for selected biomarkers, identified in other clinical studies of study drug, data may be analyzed using a model-based approach.

Population PK and PK/pharmacodynamic analyses will be detailed in a separate analysis plan.

9.7.1.7.3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Soluble, tissue, genetic and/or imaging biomarkers (Baseline and/or posttreatment) may be summarized using descriptive statistics and correlated with clinical outcomes-related endpoints for safety and/or efficacy as appropriate. Details will be included in a separate analysis plan.

9.7.1.8 Safety Analyses

Safety, using the FAS, will be assessed by monitoring and recording of all AEs including all CTCAE grades, regular monitoring of hematology and clinical chemistry, urinalysis, regular measurement of vital signs, 12-lead ECGs, and performance of physical examinations.

Adverse events and other clinical safety data will be summarized descriptively in the FAS. The incidence of TEAEs, SAEs, drug-related AEs, and AEs leading to discontinuation will be summarized in tabulation. Hematology, serum chemistry, vital sign variables and ECG will be summarized descriptively for observed values, by grade and by change from Baseline by cycle. All AEs and lab parameters will be listed.

9.7.1.8.1 Extent of Exposure

The number of cycles/days on treatment, quantity of study treatment administered, and the number of subjects requiring dose reductions, treatment interruption, treatment delay, and treatment discontinuation due to adverse events will be summarized for each study drug.

9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities

(MedDRA). Adverse events will be coded to the MedDRA (Version 17 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe by highest CTCAE grade).

The number (percentage) of subjects with TEAEs will also be summarized by relationship to each study drug and combined (Yes [related] and No [not related]).

9.7.1.8.3 LABORATORY VALUES

Clinical laboratory (ie, hematology, serum chemistry, and qualitative urinalysis) values will be evaluated for each laboratory parameter. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this protocol.

Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n[%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in CTCAE (v4.03) will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

Please see Appendix 7 for sponsor's grading of laboratory values.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, and weight) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by subject and visit.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed at the Screening Visit and during the Treatment Phase according to Table 5. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.

9.7.1.8.6 OTHER SAFETY ANALYSES

Not applicable.

9.7.1.9 Other Analyses

Any other statistical/ analytical issues will be discussed in the SAP.

9.7.2 Determination of Sample Size

The sample size is calculated using Simon's Two-Stage Design for the primary endpoint ORR assuming an ORR of 25% from this study versus an historical control of 8%. A total of approximately 31 subjects, including 16 in Stage 1, are planned to be enrolled in the study. The actual number of subjects accrued will depend on the results from Stage 1. If ≤1 responders are observed in the first 16 subjects treated (Stage 1), the enrollment will be stopped. The total sample size will be the actual number of subjects enrolled at the time of termination of the study. If ≥2 responders are observed in Stage 1, the study will proceed to Stage 2 and a total of 31 subjects will be enrolled. At least 6 responders in 31 subjects is required to claim superiority of the study treatment. This design yields a one-sided type I error of 0.0319 and the power of 0.8053 in Stages 1 and 2 combined.

9.7.3 Interim Analysis

An interim analysis may be performed by the sponsor after 16 subjects in Stage 1 have completed at least 2 tumor assessments (eg, Week 16 tumor assessments), unless discontinued due to disease progression, death or toxicity. If one or no responders are observed in the interim analysis, the study will be stopped early for futility and subjects on study at that time will continue treatment under the discretion of the investigator. If two or more responders are confirmed before the planned interim analysis and the safety profiles of both drugs are acceptable, the study will continue to Stage 2 and a formal interim analysis may be waived. There will be no enrollment gap for the interim analysis.

At interim analysis, the probabilities of early futility stopping are 0.6299 under H_0: ORR=8% and 0.0635 under H_a: ORR≥25%, respectively.

9.7.4 Other Statistical/Analytical Issues

None.

9.7.5 Procedure for Revising the Statistical Analysis Plan

The SAP will be finalized prior to the database lock in this study. Any deviation from the analysis plan described in the protocol will be documented in the SAP.

10 REFERENCE LIST

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalograms [EEGs], polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following item(s), the data recorded directly on the CRF are to be considered source data:

- Study treatment compliance (eg, the reason for dose reduction).
- Discontinuation information.
- Sampling date and time for drug concentration.
- Sampling date and time for the clinical laboratory test.
- Comments and other information on AEs (eg, severity, relationship to study treatment, outcome).

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the

protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting

the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Overview of RECIST v1.1 for Evaluation of Tumors Response

Tumor response assessments in this clinical study will use RECIST v1.1 guidelines based on the article by Eisenhauer, et al., 2009, entitled "New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)," with the exception that chest disease may not be followed using chest x-ray and must be assessed with CT. This appendix contains an overview of the RECIST v1.1 guidelines.

Baseline Tumor Assessment

Subjects are required to have measurable disease, defined as the presence of at least 1 measurable lesion, to be eligible for entry into the study. Measurable and nonmeasurable lesions are defined as:

Measurable lesions:

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

10 mm caliper measurement by clinical exam (lesions, which cannot be accurately measured with calipers, should be recorded as nonmeasurable)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be 2 times the slice thickness. In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability.

A lesion located in a previously irradiated area, or in an area previously subjected to any locoregional therapy, will be considered measurable only if there has been a documented increase in lesion size subsequent to prior treatment but before study entry.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Nonmeasurable lesions: All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with a short axis of ≥ 10 mm to < 15 mm short axis), lesions that cannot be accurately measured with calipers, and truly nonmeasurable lesions: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by PE that is not measurable by reproducible imaging techniques. Lymph nodes with a short axis <10 mm are considered nonpathological and should not be recorded or followed.

Simple cysts (cystic lesions) will not be considered malignant, and will be neither measurable nor nonmeasurable. Cystic lesions believed to be metastases may be considered measurable if they meet the general definition of measurability, but noncystic lesions are preferred as target lesions.

All baseline tumor evaluations should be performed as closely as possible to the start of treatment and never more than 4 weeks before the first dose of study treatment.

Methods of Tumor Measurement

The same imaging modality and the same technique (including use or nonuse of oral and IV contrast) should be used to characterize each identified and reported lesion at Baseline/Screening and at reassessment time points during the study. All measurements should be taken and recorded in metric notation, using calipers if clinically assessed.

Computed tomography and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Computed tomography should be performed with slices of 5 mm or less in thickness (as a general rule, lesion diameter should be no less than double the slice thickness). This applies to tumors of the chest, abdomen, and pelvis. Magnetic resonance imaging is also acceptable in certain conditions (eg, for body scans). A CT of the chest without contrast is preferred over MRI.

Bone scans, positron emission tomography (PET) scan, or plain films are not sufficient to measure bone lesions and document objective response but may be used to confirm the presence or disappearance of such lesions. Bone scans should be performed using ^{99}m-technetium-labeled polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET.

Chest x-rays should not be used for baseline assessment of the chest or for follow-up of known lesions. Chest CT should be used.

Ultrasound should not be used to measure tumor lesions.

Endoscopy and laparoscopy should not be used to measure tumor lesions.

Documentation of "Target" and "Nontarget" Lesions

Lesions are evaluated and classified at Baseline as either target or nontarget and all are then followed throughout the study.

Target Lesions:

Target lesions are all measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs. Target lesions should be selected on the basis of their size (those with the longest diameters) and their suitability for accurate repeated measurements.

The short axis (≥15 mm) of any lymph nodes selected as target lesions at Baseline will be measured and recorded at each evaluation time point, even if the nodes become nonpathological (short axis <10 mm).

The sum of the diameters of all target lesions (longest for nonnodal lesions, short axis for nodal lesions) will be calculated at Baseline and reported as the baseline sum diameter. This baseline sum of diameters will be used as the reference by which to characterize objective tumor response.

Target Lesions Too Small To Measure:

Lesions that become too small to measure during treatment should be assigned a default measurement of either 0 mm (if the investigator believes the lesion has disappeared) or 5 mm (if the lesion is believed to be present and is faintly visible).

Target Lesions That Split or Coalesce:

If a nonnodal target lesion fragments during treatment, the longest diameters of each fragment should be added together to calculate the total sum for that lesion. When lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements for each individual lesion. If the lesions are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Nontarget Lesions:

All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at Baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout Follow-up.

New Lesions:

The finding of a new lesion should be unequivocal (ie, not attributable to a change in scanning technique or imaging modality, and not thought to represent something other than a tumor). If a possible new lesion is equivocal, treatment and radiographic evaluation should continue per this protocol until confirmation of PD or until additional scans confirm the presence of a new lesion. In such a case, the date of progression will be the date of the initial scan.

A lesion identified on a Follow-up study of an anatomical location not studied as Baseline will be considered a new lesion.

Scanning with fluorodeoxyglucose positron emission tomography (FDG-PET) may be employed as a complement to CT scanning in the assessment of PD. A negative FDG-PET scan at Baseline with a positive scan during the study will be evidence of PD. If there is no FDG-PET scan at Baseline and a positive FDG-PET scan during the study, it will be considered evidence of PD if the positive FDG-PET corresponds to a new site of disease confirmed by CT scan. A positive postbaseline FDG-PET result corresponding to a preexisting site of disease with no radiographic evidence of progression will not be considered evidence of PD.

Evaluation of Response for an Individual Assessment Time Point

To determine tumor response, the sum of all target lesions is calculated at Baseline and at each subsequent assessment time point (ie, every 6 weeks until progression in this study). Each response parameter (target, nontarget, and new lesions) will be reported independently at each radiographic reading as shown below in Table 1 for target lesions and Table 2 for nontarget lesions. The investigator will then make a determination of OR for each assessment time point based on a composite evaluation of target, nontarget, and new lesions, as shown in Table 3.

Appendix 1 - Table 1 Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. All pathological lymph nodes (whether target or nontarget) must have a reduction in their short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the Baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the *smallest* sum LD recorded at Baseline or during treatment. The sum must also have an absolute increase of ≥5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the *smallest* sum LD since the treatment started
Not Evaluable (NE)	No imaging/measurement done at all or only on a subset of lesions at a particular time point; a target lesion at Baseline that is subsequently not measured or that is unable to be evaluated. Includes scans that are not performed at a specified time point to evaluate the target lesion(s).

Appendix 1 - Table 2 Evaluation of Nontarget Lesions

Complete Response (CR)	Disappearance of all nontarget lesions. All lymph nodes <10 mm (short axis)
Non-CR/Non-PD	Persistence of 1 or more nontarget lesion(s)
Progressive Disease (PD)	Unequivocal progression (substantial worsening in nontarget disease such that overall tumor burden has increased sufficiently to warrant discontinuation of therapy); unequivocal progression of existing nontarget lesions[a]
Not Evaluable (NE)	A nontarget lesion at Baseline that is subsequently not measured or that is unable to be evaluated

a: Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the site radiologist should prevail.

Appendix 1 - Table 3 Overall Response at Each Assessment Time Point for Subjects with Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	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, NE = not evaluable, PD = disease progression, PR = partial response, SD = stable disease.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time point assessment should be classified as having "symptomatic deterioration." Every effort should be made to document objective progression after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR.

Evaluation of Best Overall Response (BOR) and Confirmation of Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements [nadir] recorded since the treatment started). In general, the subject's best response assignment will

depend on the achievement of both measurement and confirmation criteria as shown in Table 4.

Confirmation: To be assigned a BOR of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In this study, a bone scan should be done within 1 week after the CR confirmatory scanning time point to exclude new bone metastases.

- The main goal of confirmation of the PR or CR objective response is to avoid overestimating the response rate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 5 weeks for this protocol.

Appendix 1 - Table 4 Best Overall Response With Confirmation

Unconfirmed response (First Time Point)	Confirmatory Response (Subsequent Time Point)	Best Overall Response of:
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD or PD[b]
CR	PD	SD or PD[b]
CR	NE	SD or NE[c]
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD[b]
PR	NE	SD[c]
NE	NE	NE

BL = baseline, CR = complete response, NE = not evaluable, PD = disease progression, PR = partial response, SD = stable disease.

a: If a CR is truly met at the first time point, then any reappearance of disease seen at a subsequent time point (including disease meeting PR criteria relative to BL) makes the disease PD at that time point.

b: Classify response as SD, provided that confirmatory scan a minimum of 5 weeks later is still "SD." Otherwise, response will be classified as PD.

c: Classify response as SD, provided that confirmatory scan a minimum of 5 weeks later is still "SD." Otherwise, response will be classified as NE.

Appendix 2 Eastern Cooperative Oncology Group Performance Status

Scale	ECOG Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG = Eastern Cooperative Oncology Group.

Adapted from Oken MM, et al. Am J Clin Oncol. 1982;5:649-55.

Appendix 3 Estimated Glomerular Filtration Rate (eGFR) Using Cockcroft and Gault Formula

$$\text{Male} \quad \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$$

$$\text{Female} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 0.85}{\text{Serum creatinine (mg/dL)} \times 72} = \text{XX mL/min}$$

Adapted from Cockcroft DW, et al. Nephron. 1976;16(1):31-41.

For serum creatinine measured in µmol/L:

$$\text{Male} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23}{\text{Creatinine (µmol/L)}} = \text{XX mL/min}$$

$$\text{Female} \quad \frac{(140\text{-age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{Creatinine (µmol/L)}} = \text{XX mL/min}$$

Appendix 4 New York Heart Association Cardiac Disease Classification

The New York Heart Association Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac subjects. Based on NYHA definitions, subjects are to be classified as follows:

Class	**NYHA Status**
Class I:	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV:	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

NYHA = New York Heart Association.

Adapted from The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. 1994:253-6.

Appendix 5 Common Terminology Criteria for Adverse Events (v4.03)

The National Cancer Institute's CTCAE v4.0 published 28 May 2009 (v4.03: June 14, 2010) provides descriptive terminology to be used for AE reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all AE terms in CTCAE version 4.0 have be correlated with single-concept, MedDRA terms.

Grades in CTCAEs v4.03 refer to the severity of the AE. Grades of 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	CTCAE Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age- appropriate instrumental activities of daily living (ADL).[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b]
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to adverse event.

CTCAE = Common Terminology Criteria for Adverse Events.

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.0. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed 02 Oct 2014).

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddramsso.com.CTCAE v4.0 is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed 02 Oct 2014).

Appendix 6 Stage Information for Renal Cell Cancer

http://www.cancer.gov/types/kidney/hp/kidney-treatment-pdq

Definitions of TNM

The TNM Staging System (tumor-node-metastasis) is the most widely used system for cancer staging in the world. The staging system for renal cell cancer is based on the degree of tumor spread beyond the kidney (Bassil B et al 1985; Golimbu M et al, 1986; Robson CJ et al 1969). Involvement of blood vessels may not be a poor prognostic sign if the tumor is otherwise confined to the substance of the kidney. Abnormal liver function test results may be caused by a paraneoplastic syndrome that is reversible with tumor removal, and these types of results do not necessarily represent metastatic disease. Except when computed tomography (CT) examination is equivocal or when iodinated contrast material is contraindicated, CT scanning is as good as or better than magnetic resonance imaging for detecting renal masses (Magnetic Resonance Imaging JAMA 1988)

Definitions of TNM

The American Joint Committee on Cancer has designated staging by TNM classification to define renal cell cancer (Edge SB et al 2010)

Table 1. Primary Tumor (T)[a]

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney.
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney.
T1b	Tumor >4 cm but not >7 cm in greatest dimension, limited to the kidney.
T2	Tumor >7 cm in greatest dimension, limited to the kidney.
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney.
T2b	Tumor >10 cm, limited to the kidney.
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia.
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia.
T3b	Tumor grossly extends into the vena cava below the diaphragm.
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava.
T4	Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland).

Table 2. Regional Lymph Nodes (N)[a]

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastases in regional lymph node(s).

Table 3. Distant Metastasis (M)[a]

M0	No distant metastasis.
M1	Distant metastasis.

Table 4. Anatomic Stage/Prognostic Groups

Stage	**T**	**N**	**M**
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2	N1	M0
	T3	N0 or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1
[a]Reprinted with permission from AJCC: Kidney. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 479-89.			

Appendix 7 Sponsor's Grading for Laboratory Values

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
				consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7080-M001-221

Study Protocol Title: A single-arm, multicenter, Phase 2 trial to evaluate efficacy and safety of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic non clear cell renal cell carcinoma (nccRCC) who have not received any chemotherapy for advanced disease

Investigational Product Name: Lenvatinib (E7080) and everolimus

IND Number: 124564

SIGNATURES

Authors:

PPD

05/08/19
Date

Oncology Business Group, Eisai, Inc

PPD

8 May 2019
Date

Oncology Business Group, Eisai, Inc

PPD

5/8/2019
Date

Oncology Business Group, Eisai, Inc

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-M001-221
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Investigational Product Name:	Lenvatinib (E7080) and everolimus
IND Number:	124564

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date

As regionally required

<Name, degree(s)>

President of Japan/Asia Clinical Research Product Creation Unit	Signature	Date