1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-G000-218
Study Protocol Title:	A Randomized, Open-Label (formerly Double-Blind), Phase 2 Trial to Assess Safety and Efficacy of Lenvatinib at Two Different Starting Doses (18 mg vs 14 mg QD) in Combination With Everolimus (5 mg QD) in Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112-8088 Japan
Investigational Product Name:	Lenvatinib (E7080), everolimus
Indication:	Renal Cell Carcinoma
Phase:	Phase 2
Approval Date(s):	29 Sep 2016 (Original Protocol) 24 Apr 2017 (Protocol Amendment 01) 12 Jul 2017 (Protocol Amendment 02) 23 May 2018 (Protocol Amendment 03) 23 Jul 2018 (Protocol Amendment 04) 18 Oct 2018 (Protocol Amendment 05) 04 Jan 2019 (Protocol Amendment 06) 07 Feb 2020 (Protocol Amendment 07) 11 Sep 2020 (Protocol Amendment 08)
IND Number:	124564
EudraCT Number:	2016-002778-11
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.

REVISION HISTORY

Revisions per Amendment 08
Date: 11 September 2020

Change	Rationale	Affected Protocol Sections
Updated the packaging section of lenvatinib. Sponsor may change the packaging from child-resistant wallets to child-resistant bottles at its discretion. No placebo will be included in bottles.	This is to allow the sponsor to adapt packaging in-line with availability and cost.	Synopsis (Study Design), Section 9.4.1 Treatments Administered Table 1- footnote, Section 9.4.3 Identity of Investigational Products, Section 9.4.10 Drug Supplies and Accountability
Updated study design to include study treatment, an off-treatment visit after the data cutoff for the primary analysis and if the study is terminated by the sponsor, study drug will be provided to subjects where commercial access is not available. Figure 8 is updated.	To outline the key assessments required for patients who remain on study post data cut-off.	Synopsis (Study Design), Section 5.1 Institutional Review Boards/Independent Ethics Committees, Section 9.1 Overall Study Design and Plan, Section 9.1.2 Randomization Phase, Section 9.1.2.2 Follow-up Period, Section 9.4.1 Treatments Administered, Section 9.4.2.2 Management of Hypertension, 9.4.2.3. Management of Proteinuria, Section 9.4.2.8 Management of Hepatoxicity, Section 9.4.6 Selection and Timing of Dose for Each Subject, Section 9.4.8.2 Prohibited Concomitant Therapy, Section 9.5.1.1 Demography and Baseline Assessments, Section 9.5.1.2 Efficacy Assessments, Section 9.5.1.3.2 Pharmacodynamic and Other Biomarker Assessments, Section 9.5.1.4 Safety Assessments, Section 9.5.1.4.1 Adverse Events and Events Associated with Special Situations, Section 9.5.1.4.2 SAEs and Events Associated with Special Situations, Section 9.5.1.4.3 Laboratory Measurements, Section 9.5.1.4.4 Vital Signs and Weight Measurements, Section 9.5.1.4.5 Physical Examinations, Section 9.5.1.4.6 Electrocardiograms, Section 9.5.1.4.7 Echocardiogram or Multiple Gated Acquisition Scan, Section 9.5.1.4.8 Pregnancy Test, Section 9.5.1.5 Other Assessments, Section 9.5.2 Schedule of Procedures/Assessments, Section

Change	Rationale	Affected Protocol Sections
		9.5.2 Schedule of Assessments after the Data Cutoff for the Primary Analysis Table 7, Section 9.5.2.1 Description of Procedures/Assessments Schedule, Section 9.5.5 Completion/Discontinuation of Subjects, Section 9.7.1.1.2 Secondary Endpoints.
Clarified the daily starting dose as lenvatinib 14 mg or 18 mg plus everolimus 5 mg		Synopsis (Sample Size Rationale), Section 7.3 Study Rationale, Section 9.2 Discussion of Study Design, Section 9.4.5 Selection of Doses in the Study, Section 9.7.2 Determination of Sample Size
Added a blood pressure assessment after the data cutoff for the primary analysis, as one blood pressure assessment is defined as the mean of 2 measurements at least 5 minutes apart. Added a vital sign measurement (resting BP, heart rate, respiratory rate and body temperature).	Updated to align with most recent program requirements.	Section 9.4.2.2 Management of Hypertension, 9.5.1.4.4 Vital Signs and Weight Measurements, Table 7.

Revisions per Amendment 07
Date: 07 February 2020

Change	Rationale	Affected Protocol Sections
Clarify that the data cutoff for the primary analysis refers to the statistical end of the study for analysis purposes (end of the Randomization Phase) and that the **End of Study** refers to the last subject last visit after which all subjects will have completed their Off-treatment visits. It further makes clear that investigational product will be provided to ongoing subjects until they have had their Off-treatment visit to transition to commercial lenvatinib or everolimus outside the study or an access program, and that subjects should follow the Schedule of Procedures and Assessments while taking investigational product. The amendment also clarifies that at the End of Study, the Sponsor (or investigator where required) will ensure that all relevant IRBs/ECs and Competent Authorities are notified about the study completion per regulatory requirements in each country or region. It is also clarified that Follow-up assessments will not be performed after the data cutoff for the primary analysis and the subject completes the Off-treatment visit assessments. The term "final" analysis is changed to "primary" analysis, because there may be analyses conducted for a final report after the primary analysis.	To clarify the End of Study definition and that investigational product will be provided to ongoing subjects until they have had their Off-treatment visit to transition to commercial lenvatinib or everolimus outside the study or an access program.	Synopsis; Sections 5.1, 9.1, 9.1.2, 9.1.2.1, 9.1.2.2, 9.3.3, 9.5.1.2, 9.5.1.4.3, 9.5.2 (Schedule of Procedures/Assessments footnotes n, s, u), 9.7, Appendix 13

Revisions per Amendment 06
Date: 04 Jan 2019

Change	Rationale	Affected Protocol Sections
Added an exploratory objective: To explore tumor response parameters (ORR_{24W}, ORR, PFS) based on blinded independent imaging review (IIR) for efficacy assessment.	After consultation, the Health Authority recommended response assessment by a blinded independent central review to corroborate the investigator assessment.	Synopsis, Section 8.3

Added process of blinded independent imaging review: Copies of all tumor assessment scans will be sent to an Imaging Core Laboratory (ICL) designated by the sponsor for blinded independent efficacy assessment. For subjects enrolled after implementation of Amendment 06, tumor assessments will be carried out following the guidelines provided by the ICL.	Change made to add the exploratory objective.	Synopsis, Section 9.5.1.2
Added exploratory endpoints: Tumor response endpoints ORR_{24W}, ORR, and PFS based on IIR assessment. These endpoints will be defined in the same way as those based on the investigator assessments.	Changed to include endpoints for the added exploratory objective.	Synopsis, Section 9.7.1.1.3
Added statistical analyses for the IIR assessments: Exploratory efficacy response endpoints ORR_{24W}, ORR, and PFS based on IIR assessment will be summarized using the same statistical methods as those used for the same response parameters based on the investigator assessments.	Changed to clarify statistical analysis methods used to assess the added exploratory endpoints.	Synopsis, Section 9.7.1.6.3

Revisions per Amendment 05
Date: 18 Oct 2018

Change	Rationale	Affected Protocol Sections
Administrative changes	Correction of minor typographical errors.	Section 1, List of Abbreviations. Section 5.2, Investigator Signature Page
Clarified that lenvatinib in plasma and everolimus in blood will be used for pharmacokinetic assessments (PK), and that PK assessments will be done using the population PK approach.	Clarification of wording.	Synopsis
Updated total sample size to approximately 338 subjects (169 subjects in each arm).	Adjusted to account for the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues.	Synopsis, Section 9.1, Section 9.3, Section 9.7.2
Clarified that HRQoL is to be assessed at Baseline, on Day 1 of each subsequent cycle, and at the Off-Treatment Visit.	Clarification of wording to ensure that HRQoL measurements are collected at the appropriate time points.	Synopsis, Section 9.5.1.5, Section 9.5.2 (Table 6)
Full Analysis set changed from primary analysis set to a secondary analysis set.	Change made as a consequence of the Oracle Interactive Voice and Web Response System (IxRS) issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses.	Synopsis, Section 9.7.1.2

Divided Per-Protocol Analysis Set into 2 data sets, Per-Protocol Analysis Set 1 and Per-Protocol Analysis Set 2. **Per-Protocol Analysis Set 1** includes all randomized subjects, but excludes the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues. **Per- Protocol Analysis Set 2** includes all randomized subjects who received at least 1 dose of study drug, had no major protocol deviations, and had both baseline and at least 1 post-baseline tumor assessment. Subjects for whom death occurred prior to the first post-baseline tumor assessment will also be included. The 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues are considered as having experienced major protocol deviations and will be excluded from Per-Protocol Analysis Set 2.	The 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues are to be excluded from efficacy data sets as these subjects are considered to have a major protocol deviation. There was an additional subject who was subsequently affected by the IxRS issue after the discovery of the 32 subjects, but because this 33rd subject received only one incorrect lenvatinib dose, this subject will not be excluded from Per-Protocol Analysis Set 1 or Per-Protocol Analysis Set 2.	Synopsis, Section 9.7.1.2
Added Per-Protocol Safety Analysis Set which includes all treated subjects minus the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses.	Synopsis, Section 9.7.1.2, Section 9.7.2
Specified that the 2 interim efficacy analyses will be performed using only Per-Protocol Analysis Set 1.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses.	Synopsis, Section 9.7.1.6, Section 9.7.2, Section 9.7.3, Appendix 13
Specified that for the final efficacy analysis, the primary analysis will be done using Per-Protocol Analysis Set 1, and the secondary efficacy analyses will be performed using the Per-Protocol Analysis Set 2 and the Full Analysis Set.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses	Synopsis, Section 9.7.1.6, Appendix 13.
Added text to clarify that the primary safety analysis using the Per-Protocol Safety Analysis Set will be performed at each interim analysis and at the final analysis, if the non-inferiority boundary of the primary efficacy endpoint is crossed.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses	Synopsis, Section 9.7.1.6, Section 9.7.2

Specified that determination of noninferiority in ORR_{24W} will be based on the results using Per-Protocol Analysis Set 1.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses	Synopsis, Section 9.7.1.6.1
Clarified that secondary efficacy analyses will be summarized descriptively using the Per-Protocol Analysis Set 1, the Per-Protocol Analysis Set 2, and the Full Analysis Set.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses	Synopsis, Section 9.7.1.6.2
Added text to specify that the safety analyses will be performed on the Per-Protocol Safety Analysis Set in addition to the Safety Analysis Set.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses	Synopsis, Section 9.7.1.6.1, Section 9.7.1.8
The statistical analysis plans for the exploratory pharmacokinetic, pharmacodynamic, and other biomarker endpoints will specify if the analyses will or will not include the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses	Synopsis, Section 9.7.1.2
Removed text from a Figure 8 label to indicate that the Randomization Phase is no longer double-blind.	Correction of a figure label error where the words “Double-blind” should have been deleted in Amendment 04.	Section 9.1
Updated text to indicate that the sites will receive lenvatinib in labeled bottles.	Clarification that once the current study drug supply is exhausted, subsequent supplies of lenvatinib will be packaged in labeled containers.	Section 9.4.3
Updated text to reflect the Per-Protocol Analysis Set 1, Per-Protocol Analysis Set 2, and Full Analysis Set will be used to summarize subject disposition and subject demographics and other baseline characteristics, and prior and concomitant therapy.	Change made as a consequence of the IxRS issues that resulted in 32 subjects receiving ≥2 incorrect lenvatinib doses.	Section 9.7.1.3, Section 9.7.1.4, Section 9.7.1.5
Clarified the definition of prior medications to indicate that these are medications that were started and stopped prior to the first dose of study drug.	Correction of error.	Section 9.7.1.5

Revisions per Amendment 04
Date: 23 Jul 2018

Change	Rationale	Affected Protocol Sections
Title	Protocol title changed to reflect change in study design.	Title page, Synopsis, Signature pages
Revised text to reflect change from double-blind to open-label study design	This is a safety-directed amendment. The protocol design was changed because of an unresolved error introduced by a programmatic update to the Oracle Interactive Voice and Web Response System (IxRS), which resulted in incorrect dose dispensing and assignment of lenvatinib to 32 treated patients between 08 Mar 2018 and 04 Apr 2018. Because an additional patient was subsequently affected, Eisai decided that it is in the best interest of the patients to unblind participants (investigators and subjects) as to all subjects' treatment assignment and to continue the conduct of the trial in an open-label fashion. This decision has been communicated to all regulatory health authorities, and all investigators received unblinding information as of 14 Jul 2018. Study enrollment will continue as planned and all subjects currently receiving study drug may continue participation in the study.	Synopsis and Sections 9.2, 9.4.1, 9.4.2.1, 9.4.4, 9.4.7, 9.5.4.5, 9.7, 9.7.1, and 9.7.3
Revised text regarding lenvatinib dispensing instructions.	To ensure that each subject is dispensed the correct dose of lenvatinib.	Sections 9.4.2.1, 9.4.3, and 9.4.4
Administrative changes	Correction of minor typographical and/or formatting errors per protocol.	List of Abbreviations; Synopsis; Sections 5.3, 7.3, 9.2, 9.4.1, 9.7.1.6.2, 9.7.2, and 9.7.3; Table 2 and Table 6; Reference List

Revisions per Amendment 03
Date: 23 May 2018

Change	Rationale	Affected Protocol Sections
Deleted the following text from Follow-up Period: "Subjects who are being followed for survival at the time of data cutoff for the primary analysis (ie, at the end of the Randomization/Treatment Phase)" The sentence is revised following this deletion, and new text is presented in bold below: "**Following the Off-Treatment Visit, subjects** will continue to be followed every 12 weeks (±1 week) for survival and PFS2, and all anticancer treatments received will be recorded until the End of Study."	Wording for Follow-up Period revised for clarity.	Protocol Synopsis (Study Design) Section 9.1.2.2 (Follow-Up Period)
End of Study (EOS) text revised and new text presented in bold below: "The End of Study is the date of the data cutoff for the final analysis when **all randomized subjects have completed Week 24 assessments or have discontinued study treatment prior to Week 24.**	Alternative wording for EOS definition is now preferred by Biostatistics Group for consistency across the program.	Protocol Synopsis (Study Design) Section 9.1 (Overall Study Design and Plan)
New paragraph added: Prior therapy must be documented by the following criteria prior to entry into study: • Any single agent therapy, and any combination of cytotoxic, hormonal, biological targeted agents, and/or humanized antibodies, scheduled to be administered as a preplanned treatment, given concomitantly, sequentially or both, is considered 1 regimen. • Planned neoadjuvant chemotherapy (to debulk the tumor prior to surgical intervention) plus postoperative adjuvant chemotherapy is considered 1 regimen.	To provide consistency in the counting of prior anticancer regimens in this study and to align with use in other protocols	Section 9.4.8.2 (Prohibited Concomitant Therapies and Drugs)

Change	Rationale	Affected Protocol Sections
• For chemotherapy: if, due to toxicity, the dosing of one or more of the components must be reduced, or one or more of the components of the regimen must be omitted, or one of the components must be replaced with another similar drug, the changed version of the original regimen is not considered a new regimen. However, if a new component, dissimilar to any of the original components, is added to the regimen, the new combination is considered a new regimen. • For prior VEGF/VEGFR-targeted agents, treatment with each agent will be counted individually, regardless of the duration of administration. • If the treatment is interrupted for surgery or radiotherapy or any other reason and then continues with an unchanged schedule and components, that treatment is considered as 1 regimen despite the interruption.		
Removed all references related to Pharmacogenomic sampling and testing from Synopsis and Protocol.	Pharmacogenomic sampling references are removed as they are no longer deemed necessary.	Synopsis (Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments; Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses) List of Abbreviations Section 5.3 (Subject Information and Informed Consent) Section 9.5.1.3.2 (Pharmacogenomic, Pharmacodynamic, and Other Biomarker Assessments) Section 9.5.2 (Table 6: Schedule of Procedures/Assessments in E7080-G0000-218) Section 9.7.1.7 (Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses) Appendix 12 (Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research)

Change	Rationale	Affected Protocol Sections
Pharmacokinetic sampling text revised and new text presented in bold below: Sparse PK samples (plasma for lenvatinib and whole blood for everolimus) will be collected from all subjects and will be analyzed using a population PK approach (PopPK). The timing for obtaining the 7 PK **sampling time points (one tube each for lenvatinib and everolimus PK)** is shown in the Schedule of Procedures/Assessments (Table 6) and Table 4.	Pharmacokinetic sampling text revised for clarity.	Section 9.5.1.3.1 (Pharmacokinetic assessments)
Revised footnote "a" in Table 6 and new text presented in bold below: "Subjects must be screened within 28 days prior to randomization. The screening assessment can serve as the baseline assessment, if performed within 72 hours before randomization. Baseline assessments may be performed on Day -1 or on C1D1 prior to randomization. **Patients randomized after the baseline assessment must have all baseline assessments reviewed prior to C1D1.** Informed consent may be obtained up to 4 weeks prior to randomization."	Clarification	Section 9.5.2 (Table 6)
Revised footnote "b" in Table 6 and new text presented in bold below: "Efforts should be made to conduct study visits on the day scheduled (±3 days). **The study visit (and safety assessments) still needs to occur regardless of a study medication hold per the visit schedule."**	Clarification	Section 9.5.2 (Table 6)
Revised footnote "k" in Table 6 and new text presented in bold below: "Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and **within 2 business days of receipt of results** for all subsequent cycles".	Clarification	Section 9.5.2 (Table 6)

Revisions per Amendment 02
Date: 12 Jul 2017

Change	Rationale	Affected Protocol Sections
The new End of Study (EOS) definition has been inserted and the paragraph has been revised to: "The End of Study is the date of the data cutoff for the final analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later. At the End of Study, subjects still receiving study treatment may continue taking lenvatinib and everolimus if available through their pharmacy (and if commercially available for that individual subject) or through an access program administered by the sponsor."	Alternative wording for EOS definition is now preferred by Biostatistics Group for consistency across the program.	Protocol Synopsis (Study Design) Section 9.1 (Overall Study Design and Plan)
Text revised and new text presented in bold below: Dose reductions and interruptions for subjects who experience lenvatinib-everolimus combination therapy-related toxicity (**except hypertension and non-infectious pneumonitis**) will be managed as described in the table below. Investigators will decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs is required. **For treatment-related hypertension and non-infectious pneumonitis, refer to Management of Hypertension (Section 9.4.2.2) and Management of Non-infectious Pneumonitis (Section 9.4.2.5) for dose modification guidelines.**	Updates made to the Dose Reduction section to clarify that Table 2 (Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity) is not intended to be used for treatment related hypertension or non-infectious pneumonitis (these sub-sections have their own independent and specific dose reduction guidelines/rules).	Protocol Synopsis (Dose Reduction) 9.4.2 (Criteria for Interruption of Treatment, Dose Reduction and Resumption of Treatment)
Removed all references related to central imaging from Synopsis and Protocol. "Copies of all tumor assessment scans will be sent to an imaging core laboratory (ICL) designated by the Sponsor for quality assessment, archival and potential future review. Tumor assessments will be carried out following the guidelines provided by the ICL."	Central imaging references are removed as they are no longer deemed necessary.	Synopsis (Efficacy Assessments) List of Abbreviations 9.5.1.2 Efficacy Assessments

Change	Rationale	Affected Protocol Sections
ICL (imaging core laboratory) from the Abbreviations List was removed. Following references related to central imaging was also deleted from the Protocol and revisions were made accordingly: Revised text: “Historical CT or MRI scans performed within 28 days of randomization but before informed consent may be used as screening scans.” Deleted: "as long as they meet minimum standards as separately defined by the ICL." Deleted: "Copies of tumor assessment scans will no longer be sent to the ICL during the Follow-up Period."		
Changed foot note "n" in the Table 6 to read: "Scans that were performed within this window but before informed consent may be used." Deleted following texts from foot note "n": "Detailed image acquisition guidelines will be provided by the imaging core laboratory." "if they were acquired consistent with the guidelines provided by the imaging core laboratory."	Central imaging references are removed as they are no longer deemed necessary.	Section 9.5.2 (Table 6, footnote “n”)
Changed Footnote "e" in the Table 6 and following text was removed: "Blood pressure assessments, in addition to those already scheduled in the protocol (as noted in the table above), will be performed: just before each scheduled PK sample (0.5 to 4 hours and 6 to 10 hours postdose on C1D1; predose and 0.5 to 4 hours and 6 to 10 hours postdose on C1D15, and predose and 2 to 12 hours postdose on C2D1)." New modified footnote "e" in the Table 6 with insertion in bold: "Assessments will include vital signs (resting BP [including date and time of measurement], HR, RR and body	There is no need to measure Blood Pressure (BP) just prior to every scheduled PK sample, but only one per protocol BP assessment on the PK draw days. It was further confirmed that it is perfectly acceptable that the Time of the BP assessment recorded is the Time the site staff first began to perform BP measures. The additional wording in footnote “e” which already appears in the body of the	Section 9.5.2 (Table 6, footnote "e”)

Change	Rationale	Affected Protocol Sections
temperature), weight, and height. Height will be measured at the Screening visit only. **One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart.** An elevated BP assessment (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg should be confirmed by a repeat assessment after a minimum of 1 hour. Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 1 and 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. A diary will be provided to the subject to capture the blood pressure evaluations between study visits. See subsection for management of hypertensive subjects."	protocol, is added here for greater emphasis.	
Deleted the words "the date" in each section of SAE/Pregnancy reporting, section of the synopsis, and protocol body. Changed to read: "no later than 24 hours from when the investigator becomes aware of the event".	Correction to make the SAE/Pregnancy reporting time frame consistent with guidelines (without unnecessary words)	Revision History Table in Protocol Amendment 01 (dated 24 Apr 2017) 9.5.4.1 (Reporting of Serious Adverse Events) 9.5.4.2 (Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding)
Following text revised in the Synopsis and Protocol, with insertions in the bold: "Concentrations of lenvatinib in plasma and everolimus in whole blood will be **pooled with existing data from other completed studies and** analyzed using a population PK approach to estimate population PK parameters **for each drug.** " Inserted new text "whenever possible using a mechanism-based approach."	PK/PD model was fixed for Ang-2, but not VEGF, on data from Study 205. Data used was from the lenvatinib arm alone and the lenvatinib+ everolimus arm from the Phase 2. This was followed by simulations and re-estimation for optimal sampling for Ang-2 in studies 218 and 307. Based on the simulation/re-estimation results, 7 biomarkers samples collected in each subject post-dosing, in addition to a baseline sample are sufficient to adequately characterise the PK/PD relationship for Ang-2.	Synopsis (Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses) 9.7.1.7 (Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses)

Change	Rationale	Affected Protocol Sections
Following statement shifted to second paragraph for alignment: "For the exposure-response relationship for biomarkers (eg, VEGF, Ang-2) data will be analyzed using a model-based approach with indirect PK/PD models."		Synopsis (Pharmacokinetic/Pharmacodynamic Analyses) 9.7.1.7.1 (Pharmacokinetic/Pharmacodynamic Analysis)
Revised following statement in the Synopsis and Protocol: "The analysis **will be** detailed in the biomarker analysis plan (BAP) and reported separately.	Based on comments from the EMA word "may" changed to "will be."	Synopsis (Biomarker Analysis) 9.7.1.7.2 (Biomarker Analyses)
Revised foot note "v" with insertions in bold: "A blood sample for biomarkers will be collected at Baseline (**pre-treatment) and** at predose at the following time points: C1D15, C2D1, **C3D1, C4D1, C5D1 and C6D1**. A sample should also be collected at the Off-treatment visit."	Removal of PD biomarker samples after cycle 6, off treatment and after post dose samples at C1D1. The optimal sample are as in the Table 6 without sampling needed on C1D1, C1 D7/8, C1 D21/22, and beyond C6 D1	Section 9.5.2 (Table 6, footnote "e")

Revisions per Amendment 01
Date: 24 Apr 2017

Change	Rationale	Affected Protocol Sections
Amended section to add additional safety results regarding dose modifications and reasons for treatment discontinuation due to toxicity.	Regulatory request from CHMP RAP	Section 7.1
Removed the following text: "The current approved dose in subjects with advanced predominant clear cell RCC following 1 prior VEGF-targeted treatment is 18 mg lenvatinib in combination with 5 mg everolimus daily." Added new text: "Lenvatinib 18 mg daily in combination with everolimus 5 mg daily is approved in the US and EU for the treatment of adult patients with advanced RCC following 1 prior VEGF-targeted therapy."	Clarification prompted by Regulatory question under Voluntary Harmonisation Procedure (VHP)	Section 9.1
Added the following text: "Lenvatinib 18 mg daily in combination with everolimus 5 mg daily is approved in the US and EU for the treatment of adult patients with advanced RCC following 1 prior VEGF-targeted therapy." Deleted the following text: "In subjects with advanced predominant clear cell RCC following 1 prior VEGF-targeted treatment, the current approved dose is 18 mg lenvatinib in combination with 5 mg everolimus."	Consistency with Section 9.1	Section 9.2
For Exclusion Criterion 15, added the text "Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by screening multigated acquisition (MUGA) scan or echocardiogram"	Regulatory request from CHMP RAP	Protocol Synopsis Section 9.3.2 - Exclusion Criterion 15
Exclusion Criterion 19, Changed "28 days" to "up to 8 weeks after study drug discontinuation"	Regulatory request under VHP for consistency with Afinitor/everolimus SmPC	Protocol Synopsis Section 9.3.2 - Exclusion Criterion 19
"Administrative reasons" changed to "other reasons"	Clarification prompted by Regulatory question under the VHP	Section 9.3.3

Deleted "hemorrhage"	Correction; there is no corresponding hemorrhage management section	Protocol Synopsis (Dose Reductions), Section 9.4.2
Revised footnote "b" in Table 2 to include hypertension. Added the following text: "For treatment-related hypertension and non-infectious pneumonitis, refer to Management of Hypertension (Section 9.4.2.2) and Management of Non-infectious Pneumonitis (Section 9.4.2.5) for dose modification guidelines."	Clarifications, since more specific dose modification guidelines for those toxicities are contained therein.	Protocol Synopsis Section 9.4.2
At the second bullet point the following text was added: "Investigators will decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs is required." At the third bullet point "Study medication" was changed to "Everolimus" and the following text was added: "Investigators will decide the probability of the event being related to 1 or both drugs as to whether discontinuation of 1 or both drugs is required."	Repeated a pre-existing sentence from paragraph 1 of Section 9.4.2 at suggestion of Protocol Steering Committee for greater clarity.	Protocol Synopsis (Management of Non-Infectious Pneumonitis), Section 9.4.2.5
Third paragraph has been changed to read: "If a subject is discontinued from the study for disease progression or toxicity, the PI may request the subject's last dispensed lenvatinib dose level if this is needed for planning of future non-study anticancer therapy. The PI will request this from the IxRS after entering confirmation that the information is needed for planning future anticancer therapy. This information will be provided by the PI to the treating medical professional."	Clarification prompted by Regulatory question from CHMP RAP	Section 9.4.7
Changed "exposure parameters" to "concentrations"	Correction	Protocol Synopsis (Pharmacokinetic Analyses), Section 9.7.1.7

Removed "sTie 2 and FGF23" from biomarker assessments	Correction to align with the PK/PD Analysis Plan	Protocol Synopsis (Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments, Pharmacokinetic/Pharmacodynamic Analyses), Section 9.5.1.3.2 Section 9.7.1.7.1
Changed footnote "e" in Table 5 to read: "If urine dipstick testing suggests a urinary tract infection, a urinalysis with microscopy and/or urine culture with sensitivities should be considered if felt clinically indicated at the institution's laboratory."	Clarification	Section 9.5.1.4.3 (Table 5, footnote "e")
Changed footnote "f" in Table 5 to read: "If urine protein by dipstick is…"	Correction	Section 9.5.1.4.3 (Table 5)
Changed footnote "b" in Table 6 from ±1 day to ±3 days	Correction	Section 9.5.2 (Table 6)
Changed from "subjects must be" to "subjects are suggested to be"	Clarification	Section 9.5.1.4.6 Section 9.5.2 (Table 6, footnote "h")
Changed footnote "q" in Table 6 to read: "…on Day 1 of each subsequent cycle starting with Cycle 2…."	Clarification	Section 9.5.2 (Table 6)
Changed footnote "k" to state that electrolyte abnormalities should be corrected before starting treatment "per the Investigator's discretion"	Clarification	Section 9.5.2 (Table 6)
Footnote "m": Deleted "PK blood samples" and replaced with "Blood samples for PK profiling lenvatinib and everolimus…" Added the following sentence at the end of footnote "m": "If possible, a blood sample for the measurement of the concentration of lenvatinib should be drawn at the first report of an SAE or a severe unexpected AE."	Repeats a similar sentence that appears in Section 9.5.1.4.2 for greater emphasis.	Section 9.5.2 (Table 6)
Removed NYHA assessments at Visits 5, 7, and 9. NYHA assessments are done only at Screening Visit only.	Correction to align footnote c of Table 6 with the Table.	Section 9.5.2 (Table 6)
28 days changed to 8 weeks	Correction for consistency with Afinitor/everolimus SmPC	Section 9.5.4.2
Changed to read: "no later than 24 hours from the date when the investigator becomes aware of the event"	Regulatory request from CHMP RAP and Regulatory request under the VHP	Section 9.5.2 (Table 6, footnote "t'') Section 9.5.4.1 Section 9.5.4.2

Changed "Functional Assessment of Cancer Therapy Kidney Syndrome Index-Disease-Related Symptoms" to "Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms"	Correction	Protocol Synopsis Abbreviation list Section 8.2 Section 9.5.1.5 Section 9.7.1.1.2
Added details on sensitivity analysis to be performed for primary endpoints to explore homogeneity of treatment effect across study centers/regions.	To address Regulatory request under the VHP (Added in response to Regulatory question under the VHP)	Clinical Protocol Synopsis and Section 9.7.1.6.1
Added new sub-section on handling of missing data for efficacy analyses	To address Regulatory request under the VHP (Added in response to Regulatory question under the VHP)	Clinical Protocol Synopsis and Section 9.7.1.6.4
Added details/explanation on estimation of non-inferiority margin	To address Regulatory request under the VHP (Added in response to Regulatory question under the VHP)	Clinical Protocol Synopsis and Section 9.7.2
Added cross-references to: Rothmann et al 2003 East 6 User Manual, 2014	Consistency, Regulatory request under the VHP	Section 9.7.2
Added cross-references to: Lan and DeMets, 1983 DeMets and Ware, 1980	Consistency, Regulatory request under the VHP	Section 9.7.3
Added the following references to the reference list: DeMets and Ware 1980 East 6 User Manual Lan and DeMets, 1983 Rothmann et al 2003	To support statistical analysis, Regulatory request under the VHP	Section 10
Changed "any other reason" to "futility"	Regulatory request under the VHP	Section 11.11
Added definitions for N, Q1, and Q3	Regulatory request under the VHP	Abbreviation list
Editorial revisions	Consistency	Throughout document

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080

Name of Active Ingredient: Lenvatinib

Study Protocol Title

A Randomized, Open-Label (formerly Double-Blind), Phase 2 Trial to Assess Safety and Efficacy of Lenvatinib at Two Different Starting Doses (18 mg vs 14 mg QD) in Combination With Everolimus (5 mg QD) in Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment

Investigator(s)

Unknown

Site(s)

Approximately 100 sites worldwide

Study Period and Phase of Development

Approximately 48-month duration

Phase 2

Objectives

Primary Objective

- To assess whether a starting dose of lenvatinib 14 mg in combination with everolimus 5 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR] at 24 weeks [ORR_{24W}]) with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg (based on treatment-emergent intolerable Grade 2, or any ≥ Grade 3 adverse events (AEs) in the first 24 weeks after randomization).

Secondary Objectives

- To assess progression-free survival (PFS).
- To assess ORR.
- To determine the tolerability and safety profile of lenvatinib in combination with everolimus.
- To assess the proportion of subjects who discontinued treatment due to toxicity.
- To assess time to treatment failure due to toxicity.
- To assess pharmacokinetic (PK) profiles of lenvatinib and everolimus during combination therapy and to assess PK and pharmacodynamic (PD) drug-drug interactions.
- To evaluate overall survival (OS).
- To evaluate the impact of disease and treatment on patients' Health-Related Quality of Life (HRQoL) as assessed by using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L.
- To evaluate the PFS after next line of treatment (PFS2).

Exploratory Objectives

- To explore tumor response parameters (ORR_{24W}, ORR, PFS) based on blinded independent imaging review (IIR) for efficacy assessment.

- To explore blood biomarkers that correlate with efficacy-related endpoints of this study.
- To develop exposure/biomarker/clinical endpoint models (whenever possible, using a mechanism-based approach) for both efficacy and safety data that will allow exploration of alternative dosing regimens with a better efficacy/safety profile than the lenvatinib 18-mg plus everolimus 5-mg dose.

Study Design

Originally, this was a multicenter, randomized, double-blind study conducted as a postmarketing requirement by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to evaluate an alternate dose regimen for lenvatinib in combination with everolimus. As of 14 Jul 2018, all ongoing subjects' treatment assignment has been unblinded to investigational site personnel, and the study will be conducted in an open-label fashion. The investigational site personnel and study subjects will be unblinded as to the treatment assignment for all newly enrolled subjects.

In subjects with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic treatment, the current approved lenvatinib dose is 18 mg daily in combination with everolimus 5 mg daily. This study will evaluate the combination of lenvatinib and everolimus in subjects with advanced predominant clear cell RCC following one prior vascular endothelial growth factor (VEGF)-targeted treatment at 14-mg starting dose of lenvatinib and allow up-titration of lenvatinib to determine whether this regimen provides comparable efficacy but has a better safety profile than the 18-mg starting dose. The 14-mg starting dose will be escalated to 18 mg if no Grade 2 (intolerable) or any ≥ Grade 3 treatment-emergent adverse events (TEAEs) that require dose reduction are observed in the first cycle (4 weeks) of treatment. If Grade 2 (intolerable) or Grade 3 or 4 TEAEs are observed, the lenvatinib dose will be reduced, as described below in the dose reduction section. Both lenvatinib and everolimus will be administered orally (PO) and once daily (QD).

Eligible subjects will have measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and will be randomly assigned to each treatment arm in a 1:1 ratio. The total sample size will be approximately 338 subjects. Randomization will follow a predefined randomization scheme based on the following stratification factors: Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate, or poor risk); and whether subjects have had a prior PD-1/PD-L1 treatment (yes or no).

Subjects will receive study treatment as continuous 28-day cycles. Treatment cycles will be counted continuously regardless of dose interruptions. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments and in the Schedule of Assessments after the Data Cutoff for the Primary Analysis. After the data cutoff for the primary analysis subjects, will be eligible to receive study treatment as continuous 56-day cycles.

Subjects will discontinue study treatment upon evidence of progressive disease, as judged by the Investigator. After disease progression, subjects will be followed for survival and PFS2 until data cutoff for the primary analysis.

This study will consist of 2 phases, the Prerandomization Phase, and the Randomization Phase with treatment continuing after the data cutoff for the primary analysis.

The **Prerandomization Phase** will last no longer than 28 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to randomization and treatment. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the sponsor.

The **Randomization Phase** will consist of a Treatment Period and a Follow-up Period. It will begin at the time of randomization of the first subject and will end at the data cutoff for the primary analysis, which is defined as when all randomized subjects complete the Week-24 tumor assessments or discontinue study treatment before Week 24. Subjects will be randomly assigned to treatment in a

1:1 ratio.

The **Treatment Period** for an individual subject will begin at the time of randomization and will end upon completion of the Off-Treatment Visit, which will occur within 28 days after the final administration of study drug. The Treatment Period consists of open-label treatment with study drug in 28-day treatment cycles that will be counted continuously regardless of dose interruptions. Serious adverse events (SAEs) and AEs must be captured for 28 days after the last dose of study drug. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments and will continue to receive study treatment until disease progression. The **Follow-up Period** will begin immediately after the Off-Treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent, or until the data cutoff for the primary analysis. Subjects who discontinue study drug treatment prior to disease progression will continue to have tumor assessments performed every 8 weeks until documentation of disease progression or initiation of another anticancer treatment. Following the Off-treatment Visit, subjects will continue to be followed every 12 weeks (±1 week) for survival and PFS2, and all anticancer treatments received will be recorded until the data cutoff for the primary analysis (ie, Follow-up ends at the end of the Randomization Phase). This information will be recorded unless this information is not allowed to be provided due to confidentiality.

If a subject discontinues study treatment and does not consent to continued follow-up, the investigator must not access confidential records that require the subject's consent. However, an investigator may consult public records to establish survival status.

While receiving investigational product, subjects should continue with the same assessments as noted in the Schedule of Assessments/Procedures.

All subjects who are still on study treatment after the data cutoff for the primary analysis (ie, at the end of the Randomization Phase) will continue to receive investigational product until they complete the Off-Treatment Visit.

After the data cutoff for the primary analysis, the **Treatment Period** will consist of **56-day treatment cycles** and an Off-Treatment Visit, where subjects still on study treatment following the data cutoff of the planned primary analysis (ie, at the end of the Randomization Phase) will continue to receive the same treatment they received during the Randomization Phase. Study treatment will continue until confirmed disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, lost to follow up or study termination by the sponsor. If the study is terminated by the sponsor, study drug (s) will be provided to subjects where commercial access is not available. Tumor assessments will be performed according to the local standard of care, and scans will no longer be required to be sent to the imaging core laboratory (ICL). The Off-Treatment Visit will occur within 28 days after the final dose of study treatment. After the data cutoff for the primary analysis, all AEs leading to study drug discontinuation and SAEs will be recorded until 28 days after the last dose of study drug.

The definition of the **End of the Study** is the last subject's last assessment (Off-Treatment Visit) after the data cutoff for the primary analysis.

The data obtained after the data cutoff for the primary analysis will be summarized and included in the CSR at the end of study as an addendum.

Number of Subjects

Approximately 338 subjects will be randomized (169 subjects in each treatment arm).

Inclusion Criteria

1. Histological or cytological confirmation of predominant clear cell RCC (original tissue diagnosis of RCC is acceptable).

2. Documented evidence of advanced RCC.
3. One prior disease progression episode on or after VEGF-targeted treatment (for example, but not limited to, sunitinib, sorafenib, pazopanib, cabozantinib, bevacizumab, axitinib, vatalanib, AV951/tivozanib) administered for the treatment of RCC. Prior PD-1/PD-L1 treatment in addition to 1 prior VEGF-targeted treatment is allowed.
4. At least 1 measurable target lesion according to RECIST 1.1 meeting the following criteria:
   - Lymph node (LN) lesion that measures at least 1 dimension as ≥1.5 cm in the short axis
   - Non-nodal lesion that measures ≥1.0 cm in the longest diameter
   - The lesion is suitable for repeat measurement using computerized tomography/magnetic resonance imaging (CT/MRI). Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of disease progression based on RECIST 1.1 to be deemed a target lesion.
5. Male or female subjects age ≥18 years (or any age >18 years if that age is considered to be an adult per the local jurisdiction) at the time of informed consent.
6. Karnofsky Performance Status (KPS) of ≥70.
7. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week before Cycle 1/Day 1.
8. Adequate renal function defined as calculated creatinine clearance ≥30 mL/min per the Cockcroft and Gault formula (Appendix 1).
9. Adequate bone marrow function defined by:
   - Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5 x 10^9/L)
   - Platelets ≥100,000/mm^3(≥100 x 10^9/L)
   - Hemoglobin ≥9 g/dL.
10. Adequate blood coagulation function defined by International Normalized Ratio (INR) ≤1.5 (except for subjects on warfarin therapy where INR must be ≤3.0 prior to randomization).
11. Adequate liver function defined by:
    - Total bilirubin ≤1.5 times the ULN except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
    - Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3×ULN (in the case of liver metastases ≤5×ULN). Subjects with bone metastases with ALP values greater than 3 times can be included.
12. Subject must voluntarily agree to provide written informed consent.
13. Subject must be willing and able to comply with all aspects of the protocol.

Exclusion Criteria

1. More than 1 prior VEGF-targeted treatment for advanced RCC.
2. Subjects with Central Nervous System (CNS) metastases are not eligible, unless they have completed local therapy for at least 4 weeks and have discontinued the use of corticosteroids for this indication or are on a tapering regimen of corticosteroids (defined as ≤10 mg prednisolone equivalent) before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
3. Active malignancy (except for RCC or definitively treated basal or squamous cell carcinoma of

the skin, or carcinoma in-situ of the cervix or bladder) within the past 24 months.

4. Any anti-cancer treatment (except for radiation therapy, see exclusion #5) within 21 days, or any investigational agent within 30 days prior to the first dose of study drug; subjects should have recovered from any toxicity related to previous anti-cancer treatment to CTC grade 0 or 1.
5. Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start.
6. Known intolerance to study drug (or any of the excipients) and/or known hypersensitivity to rapamycins (eg, sirolimus, everolimus, temsirolimus) or any of the excipients.
7. Subjects with proteinuria >1+ on urinalysis will undergo 24-h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 h will be ineligible.
8. Fasting total cholesterol >300 mg/dL (or >7.75 mmol/L) and/or fasting triglycerides level >2.5 x 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: these subjects can be included after initiation or adjustment of glucose-lowering medication.
10. Prolongation of QTc interval to >480 ms.
11. Subjects who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.
12. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib or everolimus.
13. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (eg, carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
14. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.
15. Significant cardiovascular impairment within 6 months prior to the first dose of study drug; history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke, cardiac arrhythmia associated with significant cardiovascular impairment, or left ventricular ejection fraction (LVEF) below the institutional normal range as determined by screening multigated acquisition (MUGA) scan or echocardiogram.
16. Active infection (any infection requiring systemic treatment).
17. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
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:
    - do not agree to use a highly effective method of contraception for the entire study period and for up to 8 weeks after study drug discontinuation, ie:
      - total abstinence (if it is their preferred and usual lifestyle)

- an intrauterine device (IUD) or hormone releasing system (IUS)
- a contraceptive implant
- an oral contraceptive** (with additional barrier method)

OR

- do not have a vasectomized partner with confirmed azoospermia.

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie double barrier methods of contraception, such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTES:

*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].

Must be on a stable dose of the **same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug and for the duration of the study.

Study Treatment

Originally, all study subjects, investigator site personnel, and the sponsor were blinded as to lenvatinib treatment assignment. As of 14 Jul 2018, all investigational site personnel have been unblinded as to the subjects' treatment assignment, and the study continues as an open-label trial.

Lenvatinib will be administered as 3 capsules daily. These 3 capsules will consist of 10-mg and 4-mg capsules of lenvatinib or matching placebos provided in the appropriate configuration based on their assigned dose. Investigators will provide the lenvatinib pack containing the prescribed dose and the subject will take all capsules, including any placebo. The sponsor may substitute drug supply without placebo capsules when resupplying study drug. Everolimus is provided as 5-mg tablets. In addition, the sponsor may make changes to the packaging of lenvatininb clinical supplies at their discretion. Changes may include the use of child-resistant bottles rather than child-resistant wallets. Child-resistant bottles will not include placebo. If changes to packaging are required, appropriate communication will be provided to the investigator at the study sites.

Lenvatinib 18 mg or 14 mg QD plus everolimus 5 mg QD will be taken orally in each 28-day cycle and after the data cutoff for the primary analysis in 56-day cycles. Study drug should be taken at approximately the same time each morning. Study drug may be taken in a fasting state or following a meal.

Dose Up-Titrations (14-mg Arm Only)

For subjects in the 14-mg QD (+ everolimus 5-mg) arm, if there are no intolerable Grade 2 or any ≥ Grade 3 TEAEs that require dose reduction in the first 28-day cycle (ie, the first 4 weeks of treatment), lenvatinib dose will be escalated to 18 mg QD (+ everolimus 5 mg). See the Interactive Voice and Web Response System (IxRS) Manual and revised Pharmacy Manual for further instructions.

Dose reductions for toxicity may be instituted at any time as necessary.

Dose Reductions

Adverse events will be graded using Common Terminology Criteria for Adverse Events (CTCAE)

version 4.03.

Dose reductions and interruptions for subjects who experience lenvatinib-everolimus combination therapy-related toxicity (except hypertension and non-infectious pneumonitis) will be managed as described in the table below. Investigators will decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs is required. For treatment-related hypertension and non-infectious pneumonitis, refer to Management of Hypertension (Section 9.4.2.2) and Management of Non-infectious Pneumonitis (Section 9.4.2.5) for dose modification guidelines.

Lenvatinib dose reductions occur in succession based on the previous dose level. The lenvatinib and everolimus dose may not be increased at a later date, unless the dose was mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose. Subjects in either arm will be allowed a maximum of 3 lenvatinib dose reductions for lenvatinib-related toxicity.

Refer to the subsections below for management of proteinuria, diarrhea, infections, blood glucose/lipids, hepatotoxicity, thromboembolic events, posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS), and hypocalcemia as appropriate, in addition to consulting the dose modification table below.

Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d,e] or Grade 3[f]		
First occurrence	Interrupt lenvatinib and everolimus until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose 1 level and resume everolimus at the same dose as prior to dose interruption
Second occurrence (Same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose 1 level. Dose reduction of everolimus to 5 mg every other day may be considered for Grade 3 toxicity[e]
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose 1 level. Dose reduction of everolimus for Grade 3 toxicity may be considered as follows:[e] 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 (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus	Discontinue study treatment
Grade 4[g]: Discontinue Study Treatment		

Note: For grading see CTCAE version 4.03. Collect all CTC grades of adverse events, decreasing and increasing grade.

a. An interruption of study treatment for more than 28 days will require Sponsor`s approval before treatment can be resumed.
b. Initiate optimal medical management for nausea, vomiting, hypothyroidism, hypertension and/or diarrhea before any study treatment interruption or dose reduction. For treatment-related hypertension and

non-infectious pneumonitis, refer to Management of Hypertension (Section 9.4.2.2) and Management of Non-infectious Pneumonitis (Section 9.4.2.5) for dose modification guidelines.

c. Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable.
d. Obese subjects with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1 weight loss). These subjects will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal body mass index (BMI) (if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e. For Grade 2 toxicity, resume everolimus at the same dose as prior to dose interruption. For Grade 3 toxicity, investigator will decide the probability of the event being related to one or both drugs as to whether dose modification of 1 or both drugs is required.
f. For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the Sponsor.
g. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

Lenvatinib Dose Reduction Schedule For Intolerable Toxicities

Lenvatinib dose reductions occur in succession based on the previous dose level (18, 14, 10, 8, and 4 mg/day), as shown in the table below.

Dose Reductions for Lenvatinib in Combination with 5 mg Everolimus

Current Dose (QD)	Dose Reduction
18 mg	14 mg QD
14 mg	10 mg QD
10 mg	8 mg QD
8 mg	4 mg QD

MANAGEMENT OF HYPERTENSION

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP of ≤150/90 mmHg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) is confirmed on 2 assessments a minimum of 30 minutes apart. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. After the data cutoff for the primary analysis, one BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, appropriate antihypertensive therapy should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is first observed on 2 assessments a minimum of 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib 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 ≥160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the subject has been on the same hypertensive

medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

During the Treatment Period, subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 or more frequently as clinically indicated until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 1 treatment cycle (ie, 56-day cycle). If a repeat 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 1 treatment cycle (ie, 56-day cycle).

The following guidelines should be followed for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on repeat measurements after 30 minutes:

1. Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving this.
2. For those 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.
3. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted. It should be restarted at 1 dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at an additional dose reduction only when systolic BP is ≤150 mmHg and diastolic BP is ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at a third dose reduction only when systolic BP is ≤150 mmHg and diastolic BP is ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - 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):

1. Institute appropriate medical management
2. Discontinue study treatment

MANAGEMENT OF PROTEINURIA

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments. Guidelines for assessment and management of proteinuria:

1. Grading will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to the "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity."
2. A 24-hour urine collection (within 72 hours) to verify the grade of proteinuria for protein quantitation is required in the following situations:
    - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug

- A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
- When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is 2+, 3+, or 4+

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+ or negative for 1 treatment cycle (ie, 56-day cycle).

MANAGEMENT OF DIARRHEA

An anti-diarrheal agent should be recommended to the subject at the start of study treatment and subjects should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the subject's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in the "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity" should be followed.

MANAGEMENT OF NON-INFECTIOUS PNEUMONITIS

Non-infectious pneumonitis is a recognized class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis was described in 19% of subjects taking everolimus (AFINITOR® Package Insert). Some cases were severe and on rare occasions, a fatal outcome was observed. Investigators should therefore consider a diagnosis of non-infectious pneumonitis in subjects presenting with non-specific respiratory signs and symptoms and in whom infectious, neoplastic, and other non-medicinal causes have been excluded by means of appropriate investigations.

Subjects who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms (CTCAE Grade 1) may continue study dosing without dose adjustments.

- If symptoms are moderate (CTCAE Grade 2):
  - Lenvatinib-everolimus combination therapy should be interrupted and the use of corticosteroids may be indicated until symptoms abate (resolved to CTCAE Grade 0-1) and may then be restarted at the same doses prior to study treatment interruption.
  - If Grade 2 non-infectious 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).
- If symptoms are severe (CTCAE Grade 3):
  - Lenvatinib-everolimus combination therapy should be interrupted and the use of corticosteroids may be indicated until clinical symptoms resolve (to CTCAE Grade 0-1). Investigators will decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs is required.
- If symptoms are life-threatening (CTCAE Grade 4):
  - Everolimus should be discontinued. Investigators will decide the probability of the event being related to 1 or both drugs as to whether discontinuation of 1 or both drugs is required.

MANAGEMENT OF INFECTIONS

Everolimus has immunosuppressive properties and may predispose subjects to infections. Therefore, it is important to monitor for signs and symptoms of infection and treat promptly. Dose alterations of everolimus 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 and lipids control should be optimized before starting a subject on this study.

Blood glucose will be monitored as specified in the Schedule of Procedures/Assessments. For subjects with blood glucose >ULN, a fasting (>6h, water only) blood glucose sample will be obtained. Grading according to CTCAE v4.03 will be based on the fasting blood glucose result. The choice of hypoglycemic agent should be individualized to the subject's clinical circumstances and follow standard medical practice.

Dose alterations of everolimus may be required in accordance with prescribing information.

MANAGEMENT OF HEPATOTOXICITY

Liver function tests (ALT, AST, bilirubin levels) should be monitored at baseline, every 2 weeks for the first 2 months and monthly thereafter, and as clinically indicated (see Schedule of Procedures/Assessments). If signs/symptoms indicating liver injury occur, instructions contained in the "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity" should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, the study drug 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, and deep-vein thrombosis (DVT) signs 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 the "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity" should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

MANAGEMENT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME / REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME (PRES/RPLS)

In clinical studies with lenvatinib, events of PRES/RPLS were reported in less than 1% of lenvatinib-treated subjects. PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES/RPLS, "Dose Modification Guidelines for

Lenvatinib-Everolimus Combination Treatment-Related Toxicity" should be followed.

MANAGEMENT OF HYPOCALCEMIA

Serum calcium should be monitored per the Schedule of Procedures/Assessments. Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v 4.03, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] x 0.8 + serum calcium)

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

Duration of Treatment

A subject will remain on study treatment until 1 or more of the following events occur(s):

- Progressive Disease (as determined by investigator assessment)
- Unacceptable toxicity
- Subject request
- Lost to follow-up
- Withdrawal of consent
- Termination of the study by the Sponsor
- End of study

Concomitant Drug/Therapy

The following therapies are prohibited during the Screening and Treatment Period of this study:

- Concurrent anticancer therapies such as: chemotherapy, tyrosine kinase inhibitors (TKIs), radiotherapy (except for palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases), antitumor interventions (surgical resection, thoracentesis, etc.), or immunotherapy
- Concurrent other investigational drugs
- Live vaccines while participating in the study. Examples of live vaccines include, but are not limited to the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg. Flu-Mist®) are live attenuated vaccines, and are not allowed.

For further information on the prohibited concomitant therapies for everolimus, please refer to the respective Prescribing Information.

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

For clarification, the following concomitant therapies are also allowed:

- Adjuvant hormonal therapy for history of definitively treated breast or prostate cancer
- Bisphosphonates or denosumab

- Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases will be permitted without being considered progressive disease

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

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding

Any additional procedural or patient-specific particularities should be discussed with the Sponsor.

Assessments

Efficacy Assessments

Tumor assessments will be performed using RECIST 1.1. Investigator-determined response assessments will be performed at each assessment time point and entered onto the case report form. Copies of all tumor assessment scans will be sent to an ICL designated by the sponsor for blinded independent efficacy assessment until data cutoff for the primary analysis. For subjects enrolled after implementation of Amendment 06, tumor assessments will be carried out following the guidelines provided by the ICL.

Tumor assessments (CT chest, and CT or MRI abdomen, pelvis and other known or suspected sites of disease) will be performed during the Prerandomization Phase and then during the Randomization Phase every 8 weeks (within the 8th week) until documentation of progressive disease as determined by the investigator and on a schedule as determined by the treating physician after the data cutoff for the primary analysis, but not less frequently than every 12 weeks or earlier if clinically indicated. All responses must be confirmed no less than 4 weeks following the initial indication of response. A chest x-ray or a skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

A bone scan will be performed during the Prerandomization Phase to establish a baseline (a historical bone scan performed within 6 weeks prior to randomization is acceptable), every 24 weeks after randomization, within a target of 1 week, but no more than 2 weeks following a complete response (CR) as assessed by the investigator, and as clinically indicated after the data cutoff for the primary analysis. Lesions identified on bone scans should be followed at all tumor assessment time points with cross-sectional imaging.

A brain scan will be performed at screening and as clinically indicated thereafter, and within a target of 1 week, but no more than 2 weeks following achievement of a confirmed CR. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all protocol-specified tumor assessment time points (ie, every 8 weeks). Subjects with protocol-eligible treated brain metastases should also have brain CT/MRI performed as per local standard of care. For other subjects, brain scans should be performed as clinically indicated.

Subjects going off treatment without disease progression in the Treatment Period during the Randomization Phase, will continue to undergo tumor assessments in the Follow-up Period per the above schedule until disease progression is documented, another anticancer therapy is initiated, or data cutoff for the primary analysis.

Pharmacokinetic Assessments

Sparse PK samples will be collected from all subjects and will be analyzed using the population pharmacokinetics approach.

Pharmacodynamic and Other Biomarker Assessments

Samples will be collected at protocol-specified time points as indicated in the Schedule of

Procedures/Assessments and may undergo enzyme-linked immunosorbent assay (ELISA), multiplex bead- based immunoassay, and/or other appropriate analysis procedures to explore blood biomarkers (eg, VEGF, Ang-2).

Safety Assessments

Safety assessments will consist of monitoring and recording of all AEs, including all CTCAE v4.03 grades (for both increasing and decreasing severity), and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; and the performance of physical examinations. An echocardiogram or a MUGA scan including LVEF will be performed at screening, and as clinically indicated.

Other Assessments

Health-Related Quality of Life (HRQoL) will be assessed at Baseline (prior to first dose of study drug), on Day 1 of each subsequent cycle, and at the Off-Treatment Visit. Every effort should be made to administer HRQoL surveys prior to study drug administration and before other assessments and procedures. Subjects will complete the Cancer Therapy Kidney Symptoms Index-Disease Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L instruments.

Bioanalytical Methods

Lenvatinib in plasma and everolimus in blood will be quantified by use of validated High Performance Liquid Chromatography-tandem mass spectroscopy methods.

Statistical Methods

Study Endpoints

Primary Endpoints

- Objective response rate (ORR) at Week 24 (ORR_{24W}) as assessed by the investigator according to RECIST 1.1. ORR_{24W} is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) at the Week 24 (after randomization) time point or earlier. To be considered a BOR, all responses must be confirmed no less than 4 weeks after the initial assessment of response.
- Proportion of subjects with intolerable Grade 2 and any ≥ Grade 3 TEAEs within 24 weeks after randomization (as of the Week 24 time point).

Secondary Endpoints

- Progression-free survival (PFS), defined as the time from the date of randomization to the date of first documentation of disease progression or date of death or the date of data cutoff for the primary analysis, whichever occurs first. PFS censoring rules will be defined in the statistical analysis plan (SAP) and will follow FDA guidance.
- ORR as assessed by the investigator according to RECIST 1.1 at the end of treatment. ORR is defined as the proportion of subjects with BOR of CR or PR at the end of treatment. To be considered BOR, all responses must be confirmed no less than 4 weeks after the initial assessment of response.
- Overall safety profile and tolerability of lenvatinib in combination with everolimus.
- Proportion of subjects who discontinue treatment due to toxicity, defined as the proportion of subjects who discontinue study treatment due to TEAEs.
- Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a subject discontinues study treatment due to TEAEs.
- Lenvatinib and everolimus exposure parameters and PK and PD drug-drug interactions.

- Overall survival (OS), measured from the date of randomization until date of death from any cause. In the absence of confirmation of death, subjects will be censored either at the date that the subject was last known to be alive or the date of data cutoff for the primary analysis, whichever comes earlier.
- Health-Related Quality of Life (HRQoL) will be assessed using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L instruments.
- PFS2, defined as the time from randomization to the date of disease progression after next line of therapy or death from any cause, or the date of data cutoff for the primary analysis whichever occurs first. PFS2 censoring rules will be defined in the SAP.

Exploratory Endpoints

- Tumor response endpoints ORR_{24W}, ORR, and PFS based on IIR assessment. These endpoints will be defined in the same way as those based on the investigator assessments.
- Associations between blood biomarker and efficacy-related endpoints.
- Development of exposure/biomarker/clinical endpoint models (whenever possible, using a mechanism-based approach) for both efficacy and safety data.

Analysis Sets

Full Analysis Set will include all randomized subjects. This will be a secondary analysis set for efficacy endpoints, which will be analyzed according to the treatment randomized, regardless of the treatment actually received.

Per-Protocol Analysis Set 1 will include all randomized subjects minus the 32 subjects who had received ≥2 incorrect lenvatinib doses due to IxRS issues. This will be the primary analysis set for efficacy endpoints, which will be analyzed according to the treatment randomized.

(A 33rd subject received a single incorrect lenvatinib dose due to IxRS issues, but given the brief exposure of the incorrect (slightly higher) dose before detection and correction, and because there were no adverse effects, this subject will not be excluded from this Per-Protocol Analysis Set 1.)

Per-Protocol Analysis Set 2 will include all subjects who received at least 1 dose of study drug, had no major protocol deviations, and had both baseline and at least 1 post-baseline tumor assessment. Subjects for whom death occurred prior to the first post-baseline tumor assessment will also be included. The Per-Protocol Analysis Set 2 will be a secondary analysis set for efficacy endpoints. The 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues are considered as having experienced major protocol deviations and will be excluded from the Per-Protocol Analysis Set 2.

Safety Analysis Set will include all subjects who were randomized and received at least 1 dose of study drug. This will be the analysis set for all safety evaluations, which will be analyzed according to the treatment actually received.

Per-Protocol Safety Analysis Set will include all treated subjects in Per-Protocol Analysis Set 1. This will be the primary analysis set for the primary safety endpoint, which will be analyzed according to the treatment actually received.

Pharmacokinetic (PK) Analysis Set will include all subjects who received at least 1 dose of study drug with documented dosing history and have at least 1 evaluable lenvatinib plasma or everolimus whole blood concentration data.

Pharmacodynamic Analysis Set will include all subjects who received at least 1 dose of study drug with documented dosing history and have at least 1 evaluable pharmacodynamic data.

For the Pharmacokinetic, Pharmacodynamic and other Biomarker endpoints, their respective analysis

plans will specify if the analysis set will or will not include the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues.

Quality of Life (QoL) Analysis Set will consist of all subjects who have any QoL data.

Efficacy Analyses

Analyses of Primary Endpoint:

Primary analysis of ORR_{24W} will be based on a non-inferiority test. At each interim analysis and primary analysis, the point estimate of ORR_{24W} for each treatment group (18 mg and 14 mg) will be summarized with the corresponding 95% confidence interval (CI). The odds ratio of ORR_{24W} (14 mg vs 18 mg) along with the 90% CI will be calculated using the Cochran-Mantel-Haenszel (CMH) method stratified by MSKCC prognostic groups and prior PD-1/PD-L1 treatment.

The first and second interim analysis will be performed only in the Per-Protocol Analysis Set 1. The primary analysis will be performed in the Per-Protocol Analysis Set 1 as the primary analysis set, and will also be performed in the Per-Protocol Analysis Set 2 and the Full Analysis Set as secondary analysis sets.

Non- inferiority in ORR_{24W} will be claimed if the O'Brien-Fleming non-inferiority boundary is crossed at either interim analysis or primary analysis based on the result from the Per-Protocol Analysis Set 1. If the 1-sided *P*-value is ≤0.005 at the first interim analysis, or ≤0.014 at the second interim analysis, or ≤0.045 at the primary analysis, non-inferiority in ORR_{24W} will be claimed. Futility will be claimed if the futility boundary is crossed. If the 1-sided *P*-value is ≥0.776 at the first interim analysis, or ≥0.207 at the second interim analysis, futility will be claimed. The treatment difference in ORR_{24W} for 14 mg vs. 18 mg will also be estimated along with 90% CIs based on the asymptotic normal approximation.

The safety endpoint for the primary analyses is the proportion of subjects with intolerable Grade 2 and any ≥ Grade 3 TEAEs within 24 weeks after randomization (as of the Week 24 time point). Frequency (number and percentage) will be summarized for intolerable Grade 2 and any ≥ Grade 3 TEAEs within 24 weeks after randomization by treatment. The proportions will be tested using the CMH test (2-sided alpha=0.05), stratified by MSKCC prognostic groups and prior PD-1/PD-L1 treatment. At each interim analysis and the primary analysis, if the noninferiority boundary of the primary efficacy endpoint is crossed, the analysis of the primary safety endpoint will be performed for Per-Protocol Safety Analysis Set. The proportions will also be summarized descriptively for Safety Analysis Set.

To explore homogeneity of treatment effect across centers/regions, sensitivity analyses will be conducted to adjust center/region effect for the primary endpoints of ORR_{24W} and proportion of subjects with intolerable Grade 2 and any ≥Grade 3 TEAEs within 24 weeks after randomization using logistic regression models, including center/region as a covariate.

Determination of whether 14 mg lenvatinib can be used as an alternative dosing strategy will be based on clinical judgment by the Sponsor in consultation with the independent Data Monitoring Committee (DMC) (as specified in the DMC charter) by assessing risks and benefits according to the totality of the safety and efficacy data.

Analysis of Secondary Endpoints:

All secondary efficacy endpoints will be summarized descriptively for the Per-Protocol Analysis Set 1, Per-Protocol Analysis Set 2, and Full Analysis Set. The median PFS and PFS2 will be calculated using the Kaplan-Meier (KM) product-limit estimates for each treatment group and presented with 2-sided 95% CIs. The KM estimate of PFS will also be plotted over time for each treatment group.

Point estimate of ORR and 95% CI will be summarized for each treatment arm. Odds ratio with 90% CI will be estimated using the CMH method stratified by MSKCC prognostic groups and prior PD-1/PD-L1 treatment.

The median survival time and the survival rates at 12, 18, and 24 months will be calculated using KM product-limit estimates for each treatment group and presented with 2-sided 95% CIs. The KM estimates of OS will be plotted over time.

All safety analyses will be performed on the Per-Protocol Safety Analysis Set and the Safety Analysis Set and summarized by treatment group.

The proportion of subjects who discontinue treatment due to toxicity will be summarized by frequency counts and percentages. Median, upper, and lower quintiles of time-to-treatment failure due to toxicity will be summarized for subjects who discontinue study treatment due to TEAEs.

For HRQoL analyses, summary statistics of the scores for the derived functional / symptom scales according to the scoring manual and global health status scores will be summarized by treatment arm at each time point. A separate pre-specified HRQoL analysis following FDA and EMEA PRO Guidelines will be performed and detailed in a separate SAP and HRQoL report. Scoring of EQ-5D-3L and derivation of utility for health economic analysis will also be accomplished in a separate analysis and described in a separate HRQoL report.

Analysis of Exploratory Endpoints:

All exploratory endpoints will be summarized descriptively. Exploratory efficacy response endpoints ORR_{24W}, ORR, and PFS based on IIR assessment will be summarized using the same statistical methods as those used for the same response parameters based on the investigator assessments.

Pharmacokinetic, Pharmacodynamic and Other Biomarker Analyses

Pharmacokinetic Analyses

Lenvatinib and everolimus concentrations will be summarized by use of descriptive statistics and plotted as appropriate for each treatment group.

Concentrations of lenvatinib in plasma and everolimus in whole blood will be pooled with existing data from other completed studies and analyzed using a population PK approach to estimate population PK parameters for each drug. The analyses will be detailed in a separate analysis plan.

Pharmacokinetic/Pharmacodynamic Analyses

Lenvatinib and everolimus exposure parameters (AUC or concentration at the time of the event or cumulative AUC, as appropriate) derived from the population PK analysis will be related to biomarker, safety, and efficacy data using a model-based approach. For some PK/PD analyses, data from this study will be pooled with data from the Phase 2 Study E7080-G000-205 (Study 205).

For the exposure-response relationship for biomarkers (eg, VEGF, Ang-2) data will be analyzed using a model-based approach with indirect PK/PD models.

For efficacy, a tumor growth inhibition model based on longitudinal tumor size measurements of target lesions will be included. Study drug exposure for lenvatinib and everolimus and/or measured biomarkers (eg, VEGF, Ang-2) will be investigated as predictors and/or correlations with tumor burden changes in the tumor growth inhibition model, whenever possible using a mechanism-based approach.

Other analyses will include logistic regression analysis for ORR_{24W}, KM plots of PFS data, and Cox-regression analysis. For the Cox-regression analysis of PFS, adjustment will be made for subject's baseline characteristics or tumor-related features. In addition to lenvatinib and everolimus exposure, changes in biomarker concentrations and/or tumor burden will be related to PFS, whenever possible using a mechanism-based approach.

For the exposure-response relationship of safety, the model-based analysis will include the following AEs: hypertension (systolic and diastolic BP), triglyceridemia (and cholesterolemia), glycemia, proteinuria, weight loss, fatigue, nausea, vomiting and diarrhea. For hypertension, triglyceridemia (and cholesterolemia) and glycemia, data will be analyzed using an indirect-response model. For proteinuria, urine dipstick and/or 24-hour urine data will be analyzed using a longitudinal categorical

logistic regression analysis with Markov element. For weight loss, fatigue, nausea, vomiting, and diarrhea, data will be analyzed using a longitudinal categorical logistic regression analysis. For time to treatment discontinuation due to an AE and time to first dose reduction, KM plots stratified by lenvatinib exposure will be prepared.

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

Biomarker Analysis

The effect of lenvatinib and everolimus combination treatment on exploratory biomarkers will be summarized by treatment group. Associations between clinical outcomes and baseline biomarker levels, and/or change in levels from baseline will be explored. The analysis will be detailed in the biomarker analysis plan (BAP) and reported separately.

For exploratory endpoints, Pharmacokinetic, Pharmacodynamic and Other Biomarker endpoints, their respective analysis plans will specify if the analyses will and will not include the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues.

Safety Analyses

All safety analyses will be performed by treatment group for the Per-Protocol Safety Analysis Set and Safety Analysis Set. The incidence of TEAEs, intolerable Grade 2 TEAEs that lead to dose interruption, dose reduction, or drug discontinuation, and SAEs will be summarized and rates will be summarized descriptively.

Time to treatment discontinuation due to an AE, number of dose reductions, and time to first dose reduction will be summarized.

Laboratory test results, vital signs and their changes from baseline, and 12-lead ECG results will be summarized using descriptive statistics. Abnormal values will be flagged. Prior and concomitant medications, medical/surgical history and subject demographics will be summarized and listed.

Interim Analyses

Safety and efficacy monitoring will be performed by an independent DMC. The function and membership of the DMC will be described in the DMC charter. Minutes from the open meetings of the DMC will be provided to regulatory agencies, if requested.

Two interim analyses will take place when 150 and 200 total subjects in Per-Protocol Analysis Set 1 have completed 24 weeks follow-up or discontinue earlier. Each interim analysis will test both non-inferiority and futility of the 14-mg arm ORR_{24W} compared with the 18-mg arm ORR_{24W}. An O'Brien-Fleming stopping boundary will be used for non-inferiority. An interpolated non-binding stopping boundary will be used for futility.

Sample Size Rationale

The objective of the study is to assess whether a starting dose of lenvatinib 14 mg QD in combination with everolimus 5 mg will provide comparable efficacy with an improved safety profile compared with lenvatinib 18 mg in combination with everolimus 5 mg. Determination of whether 14 mg lenvatinib can be used as an alternative dosing strategy will be based on clinical judgment by the Sponsor in consultation with the independent DMC (as specified in the DMC charter) by assessing risks and benefits according to the totality of data at either of the interim or primary analyses. Nevertheless, the sample size is guided by the plan of testing non-inferiority on primary efficacy endpoint and superiority on primary safety endpoint. The details and assumptions are provided below.

Sample size is based on detecting both the non-inferiority of ORR_{24W} and superiority of the primary safety endpoint of the proportion of subjects with intolerable Grade 2 and any ≥ Grade 3 TEAEs within 24 weeks after randomization in comparison of 14-mg arm to 18-mg arm.

Non-inferiority of ORR_{24W} comparing the 14-mg arm to the 18-mg arm:

Based on the assumption from Study E7080-G000-205 that the confirmed ORR for 18 mg lenvatinib + 5 mg everolimus arm is 37% (19 responders out of N=51) vs. 6% for the everolimus arm (3 responders out of N=50), the 95% CI comparing everolimus vs. lenvatinib 18 mg + everolimus arm is (0.029, 0.395). The non-inferiority margin is chosen to ensure that a reasonable fraction of the lenvatinib 18 mg + everolimus vs. everolimus treatment effect is preserved. A 70% retention of the treatment effect of lenvatinib 18 mg + everolimus vs. everolimus is used for this design. Following the approach in Rothmann et al. (2003), using the 95% CI upper limit method based on logarithm of the odds ratio, the non-inferiority margin is estimated as $\exp((1-\delta) * (upper\ limit\ of\ 95\%\ CI\ of \log odds\ ratio\ (eve\ /lenv\ 18\ mg+\ eve\ )))$,

where $0 < \delta < 1$ is the retention rate.

To retain 70% of the lenvatinib 18 mg + everolimus vs. everolimus treatment effect, the non-inferiority margin of the odds ratio is estimated to be $\exp((1-0.7) * log(0.395)) = 0.76$ (ie, Ha: OR (14 mg/18 mg)> M).

The table below lists the non-inferiority margins on the scale of difference in ORR_{24W} between the lenvatinib 14-mg + everolimus arm and the lenvatinib 18-mg + everolimus arm corresponding to a 0.76 non-inferiority margin on the odds ratio scale for a different ORR_{24W} in the lenvatinib 18-mg +everolimus arm.

ORR_{24W} in the lenvatinib 18-mg arm	Non-inferiority margin on difference scale (lenvatinib 14-mg arm - lenvatinib 18-mg arm)
10%	-0.02
20%	-0.04
30%	-0.05
40%	-0.06
50%	-0.07
60%	-0.07

Two interim analyses will take place when 150 and 200 total subjects in the Per-Protocol Analysis Set 1 have completed 24 weeks follow-up or discontinue earlier. Each interim analysis will test both non-inferiority and futility of the 14-mg-arm ORR_{24W} compared to the 18-mg-arm ORR_{24W}. An O'Brien-Fleming stopping boundary will be used for non-inferiority. An interpolated non-binding stopping boundary will be used for futility, which will spend $\beta = 0.005$ and $\beta = 0.10$ at the first and second interim analysis, respectively. Assuming 37% ORR_{24W} in the lenvatinib 18-mg arm and 45% ORR_{24W} in the lenvatinib 14-mg arm, and adjusting for the interim analyses, a total of 306 subjects (153 per arm) is required to achieve 80% statistical power at one-sided $\alpha = 0.05$.

The stopping boundaries on the *P*-value scale and the cumulative error probabilities spent at each interim analysis and primary analysis are shown in the table below. For example, at the second interim analysis, non-inferiority in ORR_{24W} will be claimed if the *P*-value is ≤0.014; futility will be claimed if the *P*-value is ≥0.207.

Analysis #	**Cumulative α Spent**	**Efficacy Boundary (*P*-value)**	**Cumulative β Spent**	**Futility Boundary (*P*-value)**
Interim Analysis #1	0.005	0.005	0.005	0.776
Interim Analysis #2	0.015	0.014	0.10	0.207
Primary Analysis	0.05	0.045	0.2	0.045

Superiority of primary safety endpoint comparing the 14-mg arm to the 18-mg arm:

At each interim analysis and the primary analysis, safety will be evaluated if the non-inferiority

boundary is crossed. Assuming 75% of subjects with intolerable Grade 2 or above TEAEs within 24 weeks after randomization in the 18-mg arm, with a total of 306 subjects, a superiority test at 2-sided $\alpha = 0.05$ will give 80% statistical power to detect a 15% drop in proportion of subjects with intolerable Grade 2 or above TEAEs within 24 weeks after randomization in the 14-mg arm.

In consideration of both the primary efficacy and safety endpoints, a total of approximately 306 subjects was originally planned to be randomized in a 1:1 ratio to both treatment arms. Since there were 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues, the number of subjects to be randomized will be increased by 32 to a total of approximately 338. Thus, approximately 306 subjects will be included in the Per-Protocol Analysis Set 1. Randomization will be stratified by MSKCC prognostic groups (favorable, intermediate, and poor risk) and whether subjects have had a prior PD-1/PD-L1 treatment (yes or no).

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE(s)	adverse event(s)
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BOR	Best overall response
BP	blood pressure
CA	Competent Authority
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT/MRI	computerized tomography/magnetic resonance imaging
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
CYP	cytochrome P
DMC	data monitoring committee
DOR	duration of response
EBRT	external beam radiotherapy
ECG	electrocardiogram
EMA	European Medicines Agency
EORTC	European Organization for the Research and Treatment of Cancer
EuroQol	European Quality of Life
FDA	Food and Drug Administration

Abbreviation	Term
FKSI-DRS	Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms
GCP	Good Clinical Practice
HRQoL	Health-Related Quality of Life
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICL	imaging core laboratory
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IxRS	Interactive voice and web response system
KM	Kaplan-Meier
KPS	Karnofsky Performance Status
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MSKCC	Memorial Sloan-Kettering Cancer Center
MUGA	multigated acquisition scan
N	number of subjects
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	objective response rate
ORR_{24W}	objective response rate at 24 weeks
OS	Overall survival
PRES/RPLS	posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome
PD	progressive disease or pharmacodynamic
PFS	progression-free survival
PFS2	progression-free survival after next line of therapy
PI	principal investigator or package insert
PR	partial response
PRO	patient-reported outcomes

Abbreviation	Term
PK	pharmacokinetics
PO	orally (per os)
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOPs	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TEAE(s)	treatment-emergent adverse event(s)
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WHO	World Health Organization

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 ICH E6 (Good Clinical Practice), 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) (or if regionally required, the head of the medical institution) 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 (or if regionally required, the head of the medical institution) 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 (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) 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.

The data cutoff for the primary analysis will occur at the end of the Randomization Phase, which is defined as the time the last subject enrolled completes the Week-24 tumor assessments or discontinues study treatment before Week 24. Subjects will continue to receive investigational product until they complete the Off-treatment visit. All subjects who are still on study treatment after the data cutoff for the primary analysis (ie, at the end of the Randomization Phase) will continue to receive investigational product until they complete the Off-Treatment Visit. The definition of the **End of Study** is the last subject's last assessment (Off-Treatment Visit) after the data cutoff for the primary analysis. At the End of Study, the Sponsor (or investigator where required) will ensure that all relevant IRBs/ECs and Competent Authorities are notified about the study completion per regulatory requirements in each country or region.

The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

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 Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2013)
- 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 Technical Requirements for 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
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject 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 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, 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, and after the subject 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 at the

Screening Visit 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.

The subject 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

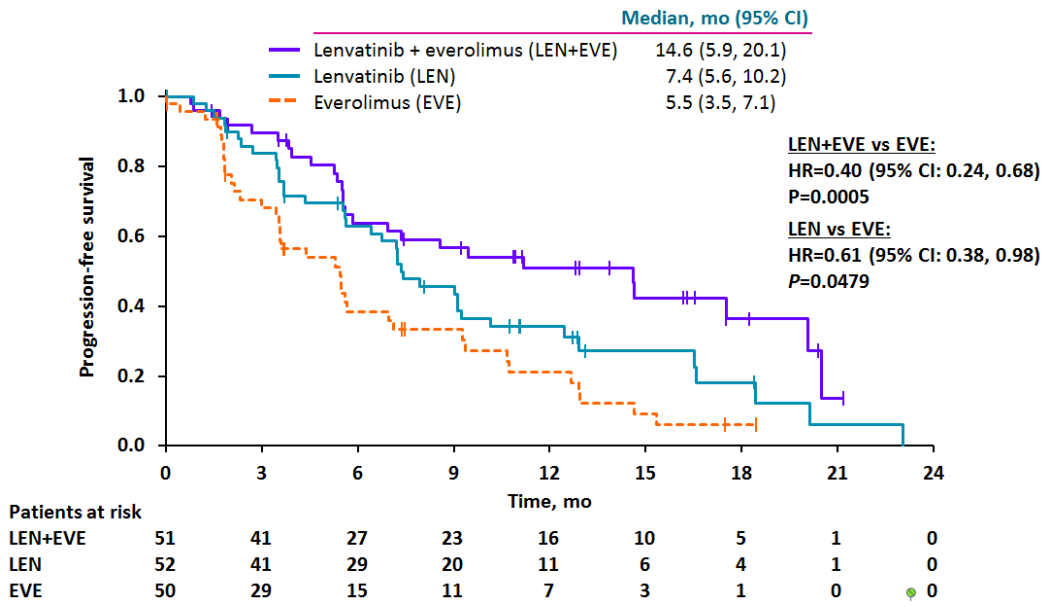
This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 100 investigational site(s) worldwide.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organizations (CROs) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION AND STUDY RATIONALE

7.1 Clinical Results Obtained with the Combination of Lenvatinib with Everolimus

The safety and efficacy of lenvatinib and everolimus in combination was investigated in Study E7080-G000-205 (hereafter referred to as "Study 205") in subjects with predominant clear cell renal cell carcinoma (RCC) following 1 prior vascular endothelial growth factor (VEGF)-targeted treatment. The combination significantly prolonged progression-free survival (PFS) compared with either agent as monotherapy, as shown in the Kaplan-Meier (KM) (Kaplan and Meier, 1958) curve presented in Figure 1.



Source: Study 205 CSR, Figure 4

Figure 1 Kaplan-Meier Plot Of Progression-Free Survival – Full Analysis Set (Phase 2)

The treatments studied were lenvatinib plus everolimus (18 mg plus 5 mg, respectively, once daily [QD]), lenvatinib (24 mg QD), and everolimus (10 mg QD).

The safety profile for lenvatinib plus everolimus was consistent with the known toxicities of each individual agent, with no unexpected treatment-emergent adverse events (TEAEs) observed (AFINITOR® Package Insert and LENVIMA® Package Insert). The most common TEAEs of any grade in the lenvatinib plus everolimus arm were diarrhea and fatigue or asthenia. Grade 3 and 4 AEs occurred in 36/51 (71%) of the subjects in the lenvatinib plus everolimus cohort. The most common Grade 3 or 4 TEAE in the lenvatinib plus everolimus cohort was diarrhea (10/51 [20%]).

The percentage of subjects with lenvatinib dose reduction and/or dose interruption was similar in the combination and lenvatinib arms (84.3% and 78.8%, respectively). The percentage of subjects with study treatment discontinuation was similar in both lenvatinib containing arms (23.5% for the combination and 25.0% for the lenvatinib arm).

Diarrhea and vomiting were the most frequently reported AEs that led to dose reduction and/or interruption in the combination arm. These events resulted in dose reduction and/or interruption more often in the combination than in the lenvatinib arm: 41.2% vs 28.8%, respectively, for diarrhea and 19.6% vs 5.8%, respectively, for vomiting.

The percentages of subjects with study treatment discontinuation due to AEs were similar in both the combination and lenvatinib arms (23.5% and 25.0%, respectively) and were approximately 2-fold higher than in the everolimus arm (12.0%).

The percentage of subjects who had everolimus dose interruptions due to AEs was higher in the combination arm than in the everolimus arm (76.5% vs 54.0%), while the percentage of subjects with everolimus dose reductions was higher in the everolimus arm (26.0%) than in the combination arm (2.0%). The percentage of subjects with study treatment discontinuation due to AEs was higher in the combination arm (23.5%) compared to everolimus arm (12.0%).

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 Results of Exposure-Response Analyses for Lenvatinib plus Everolimus

The intent of the current study is to determine whether a different dosing regimen can maintain the significant efficacy (objective response rate at 24 weeks; ORR_{24W}) while reducing the frequency of Grade 3 and 4 AEs. To that end, using data from Study 205, Eisai and the FDA have collaboratively developed a tumor-growth PK/PD model, as depicted in Figure 2, which incorporates tumor suppression by both lenvatinib and everolimus and tumor resistance to lenvatinib for the purpose of evaluating, in terms of safety and efficacy, the effect of (1) lower lenvatinib starting doses, (2) lenvatinib drug holidays (eg. 2-week on/1-week off), and (3) different lenvatinib starting doses with the option of up-titrations of the lenvatinib dose. The model (shown below) incorporates terms for the natural growth rate of the clear cell RCC tumors and the growth suppressing effects of both lenvatinib and everolimus. Additionally, an exposure-AE binary model was developed for the relationship between exposure to lenvatinib and any AE leading to drug reduction, interruption or discontinuation (data on file; Modeling and Simulation Report CPMS-E7080-008ADD).

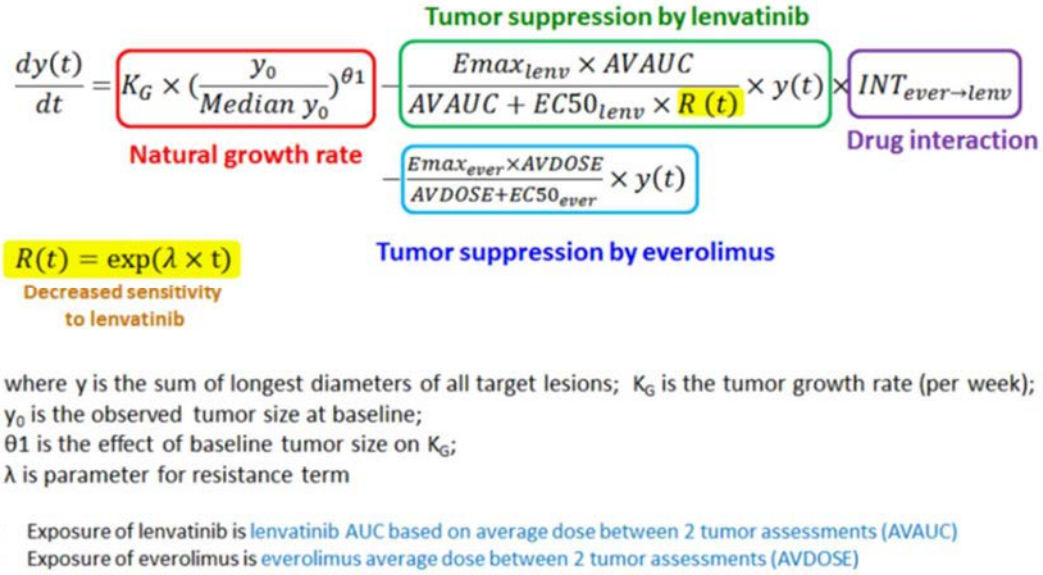
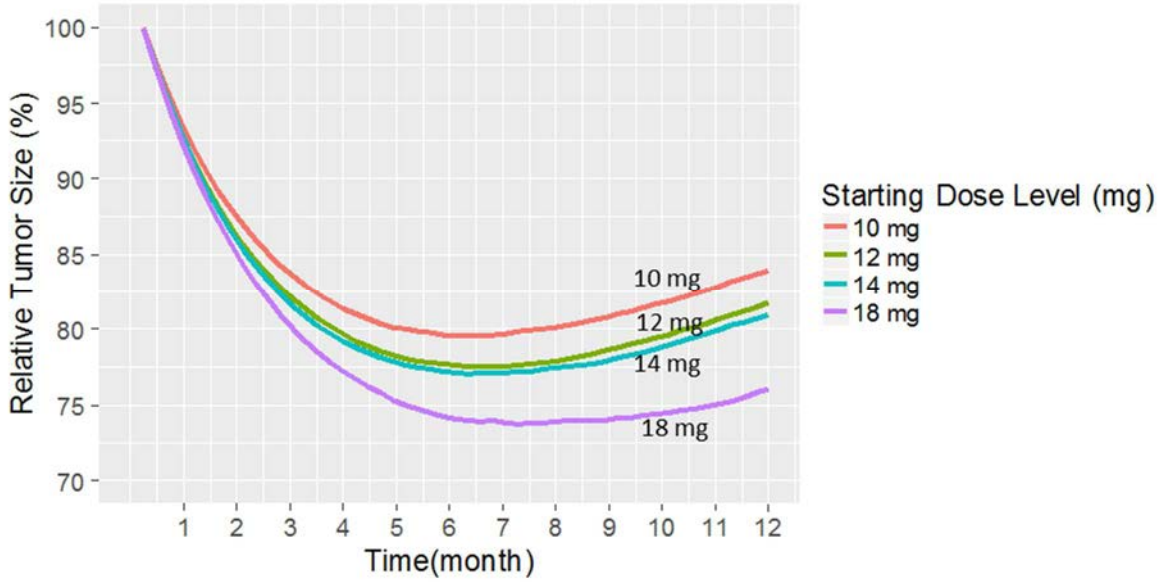


Figure 2 Tumor Growth Inhibition PK/PD Model

The FDA and Eisai both utilized these models to explore various exposure-response analyses for the time course of tumor burden (size) and dose-altering AEs to aid in the design of the current study.

The three cases modeled were: (Case 1) where lenvatinib starting doses less than 18 mg QD in combination with 5 mg QD everolimus were administered and doses were reduced as necessary to control AEs; (Case 2) where a lenvatinib drug holiday was incorporated into the dosage regimen; and (Case 3) Case 1 with the additional caveat that a subject's lenvatinib dose could be subsequently raised as long as the subject tolerated the current dose. Note that Study 205 followed Case 1.

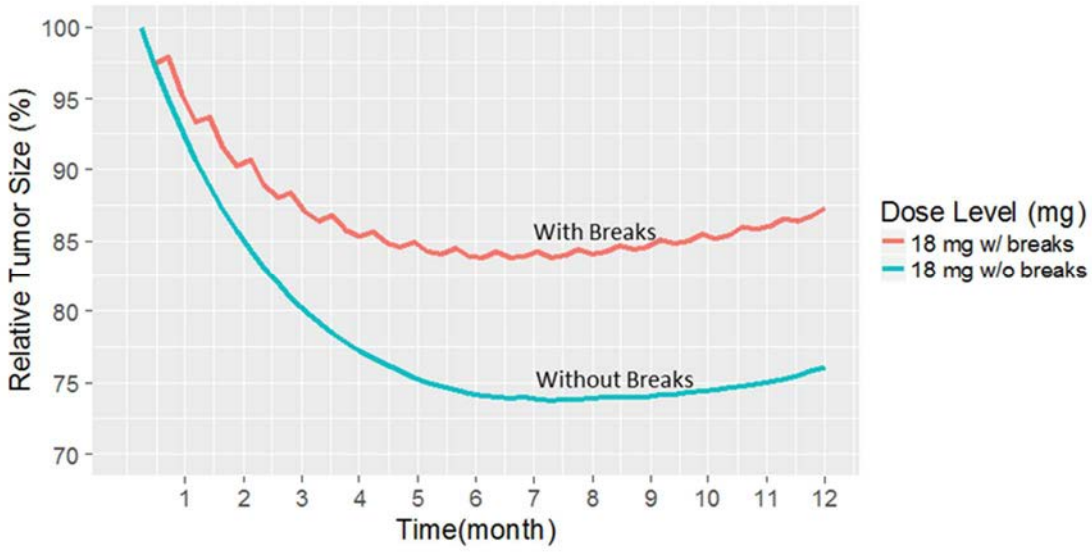
The modeling results showed that in Case 1, lenvatinib daily doses less than 18 mg were less effective, ie, the simulated percent reduction in tumor size was less and occurred later than with the 18-mg dose (see Figure 3), and the predicted ORR_{24W} was lower.



* In combination with 5 mg QD everolimus.

Figure 3 Case 1 – Effect Of Starting Dose Levels Less Than 18 Mg Lenvatinib* With No Allowance For Lenvatinib Dose Escalation

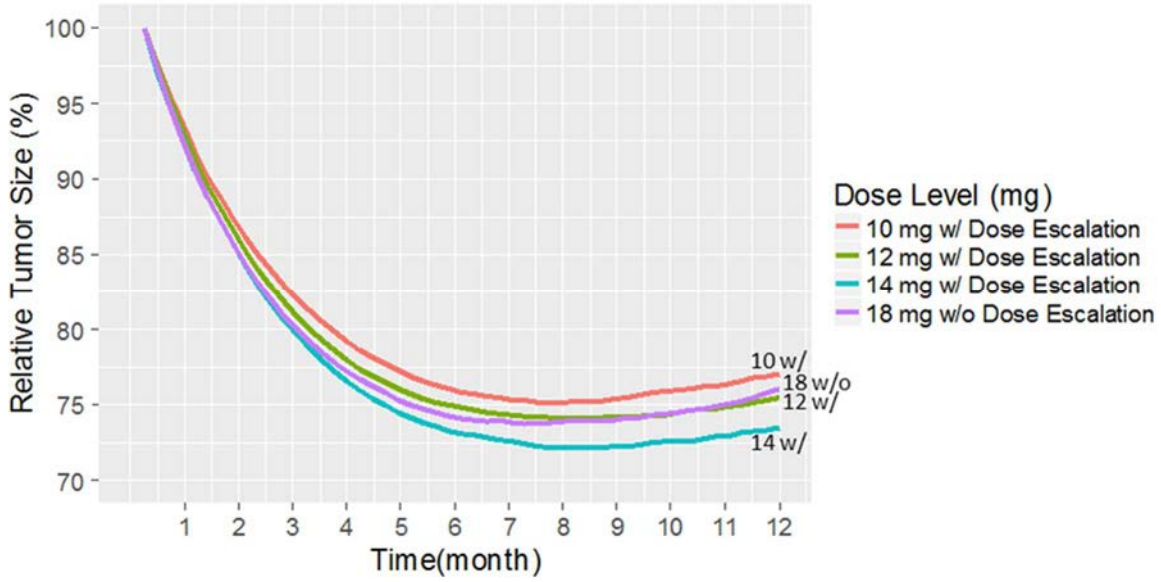
In Case 2 (see Figure 4), the efficacy of regimens utilizing a lenvatinib drug holiday proved less effective than continuous dosing, and the predicted ORR_{24W} was lower.



* In combination with 5 mg QD everolimus.

Figure 4 Case 2 - Simulated Average Tumor Reductions With Starting Dose Of 18 Mg Lenvatinib* With And Without Drug Holiday (One Week Break In Lenvatinib Administration After Two-Week Continuous Lenvatinib Administration With Continuous Everolimus Administration)

In Case 3 (see Figure 5), the efficacy of regimens that utilize lower starting doses (ie, 12 mg or 14 mg) but allow up titration of doses showed equivalent or superior tumor reduction and comparable predicted ORR_{24W} to an 18-mg starting dose that only allowed dose reduction of lenvatinib.



* In combination with 5 mg QD everolimus.

Figure 5 Case 3 - Simulated Average Tumor Reductions With Lenvatinib* Dose Escalation

Simulations of the 2 dose regimens to be investigated in this study suggest that the 14-mg lenvatinib starting dose (while maintaining the 5-mg QD everolimus dose) can also result in fewer dose reductions (see Figure 6).

Starting Dose: 18 mg w/o dose escalation **Starting Dose: 14 mg w/ dose escalation**

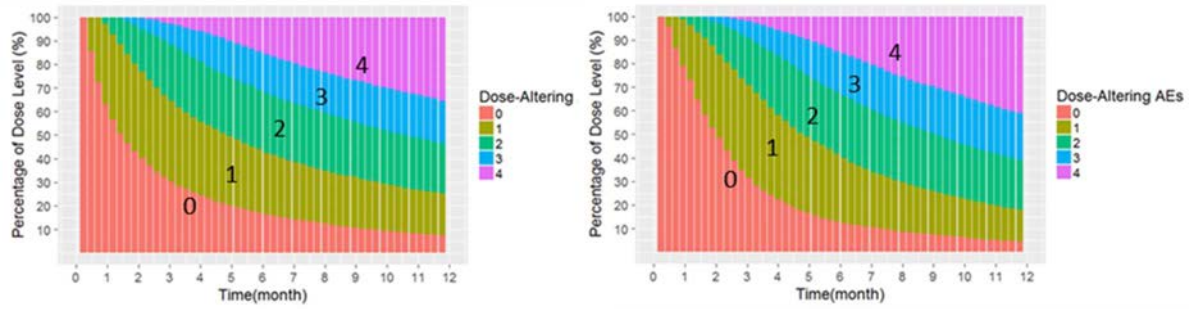


Figure 6 Simulated Average Dose And Proportion Of Subjects With At Least One Dose Modification During 24 Weeks (Median Of 500 Replicates For 46 Subjects)

The utility of allowing a second 4-mg up-titration of the lenvatinib dose to 22 mg was also modeled. As shown in Figure 7, there was no added benefit to increasing the dose to 22 mg from the 14-mg starting dose:

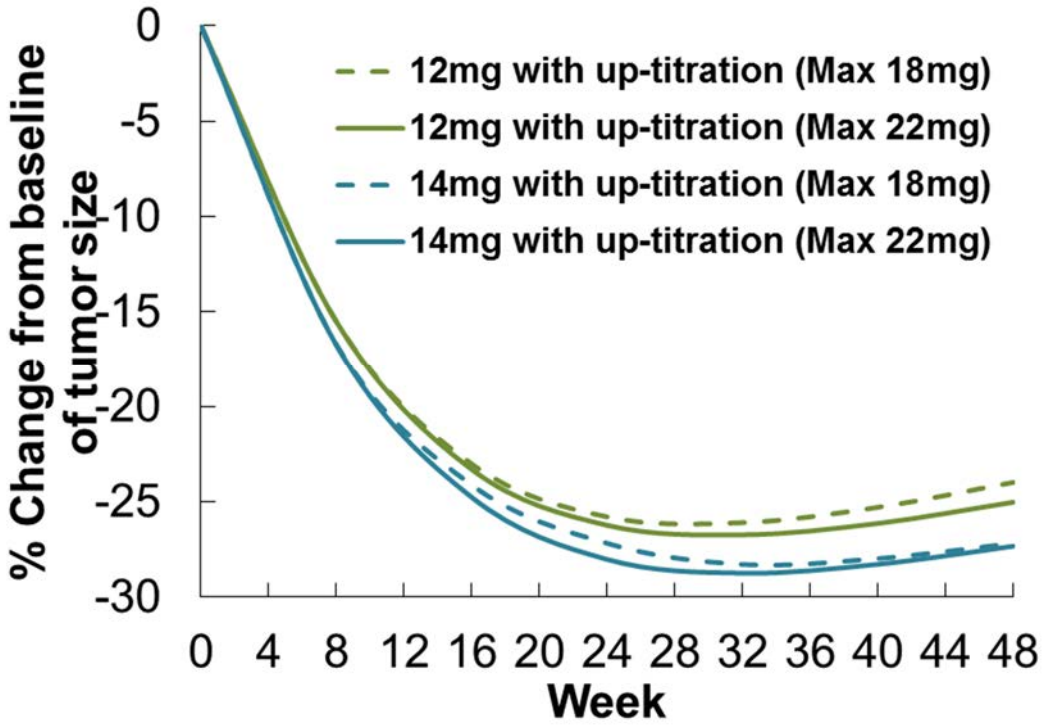


Figure 7 Utility of Allowing a Second 4-mg Up-titration of the Lenvatinib Dose to 22 mg

7.3 Study Rationale

Based on the results of Study 205 and the exposure-response models, the current Study 218 was designed as a 2-arm study to investigate daily starting doses of lenvatinib 14 mg or lenvatinib 18 mg both in combination with everolimus 5 mg in subjects with RCC. The reference 18-mg lenvatinib dose regimen will only allow reduction of the dose as necessary to control AEs. In contrast, the 14-mg lenvatinib dose regimen will require one 4-mg/day increase (ie, to 18 mg) on Day 1 of Cycle 2, if the subject is tolerating the 14-mg dose (while also allowing reduction of the dose whenever necessary to control AEs). The objective of the study is to determine whether the lower lenvatinib starting dose regimen provides equivalent efficacy (as assessed by ORR_{24W}) with increased safety to the subjects with RCC.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to assess whether a starting dose of lenvatinib 14 mg in combination with everolimus 5 mg QD will provide comparable efficacy (based on ORR_{24W}) with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg (based on treatment-emergent intolerable Grade 2 or any ≥ Grade 3 AEs in the first 24 weeks after randomization).

8.2 Secondary Objectives

The secondary objectives of the study are:

- To assess progression-free survival (PFS)
- To assess ORR
- To determine the tolerability and safety profile of lenvatinib in combination with everolimus
- To assess the proportion of subjects who discontinued treatment due to toxicity
- To assess time to treatment failure due to toxicity
- To assess pharmacokinetic (PK) profiles of lenvatinib and everolimus during combination therapy and to assess PK and pharmacodynamics (PD) drug-drug interactions
- To evaluate overall survival (OS)
- To evaluate the impact of disease and treatment on patients' Health-Related Quality of Life (HRQoL) as assessed by using the Functional Assessment of Cancer Therapy - Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L
- To evaluate the PFS after next line of treatment (PFS2)

8.3 Exploratory Objectives

The exploratory objectives of the study are:

- To explore tumor response parameters (ORR_{24W}, ORR, PFS) based on blinded independent imaging review (IIR) for efficacy assessment
- To explore blood biomarkers that correlate with efficacy-related endpoints of this study
- To develop exposure/biomarker/clinical endpoint models (whenever possible, using a mechanism-based approach) for both efficacy and safety data that will allow exploration of alternative dosing regimens with a better efficacy/safety profile than the lenvatinib 18-mg plus everolimus 5-mg dose

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

Originally, E7080-G000-218 was designed as a multicenter, randomized, double-blind study, conducted as a postmarketing requirement of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to evaluate an alternate dose regimen for lenvatinib in combination with everolimus. As of 14 Jul 2018, all ongoing subjects' treatment assignment has been unblinded and the study will be conducted in an open-label fashion. The investigational site personnel will be unblinded as to treatment assignment for all newly enrolled subjects. Lenvatinib 18 mg daily in combination with everolimus 5 mg

daily is approved in the US and EU for the treatment of adult patients with advanced RCC following 1 prior VEGF-targeted therapy.

This study will evaluate the combination of lenvatinib and everolimus at a 14-mg starting dose of lenvatinib and allow up-titration of lenvatinib to determine whether this alternate dose regimen provides comparable efficacy but has a better safety profile than the 18-mg starting dose in this subject population. The 14-mg starting dose will be escalated to 18 mg if no Grade 2 (intolerable) or any ≥ Grade 3 TEAEs that require dose reduction are observed in the first cycle (4 weeks) of treatment. If Grade 2 (intolerable) or Grade 3 or 4 TEAEs are observed, the lenvatinib dose will be reduced, as described in the dose reduction section (Section 9.4.2). Both lenvatinib and everolimus will be administered orally (PO) and daily (QD).

Eligible subjects will have measurable disease according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and will be randomly assigned to each treatment arm in a 1:1 ratio. The total sample size will be approximately 338 subjects. Randomization will follow a predefined randomization scheme based on the following stratification factors: Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate, or poor risk); and whether subjects have had a prior PD-1/PD-L1 treatment (yes or no).

Subjects will receive study treatment as continuous 28-day cycles. Treatment cycles will be counted continuously regardless of dose interruptions. Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 6) and in the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). After the data cutoff for the primary analysis subjects will be eligible to receive study treatment as continuous 56-day cycles.

Subjects will discontinue study treatment upon evidence of progressive disease, as judged by the investigator. After disease progression, subjects will be followed for survival and PFS2 until the data cut-off for the primary analysis.

This study will consist of 2 phases, the Prerandomization Phase and the Randomization Phase with treatment continuing after the data cutoff for the primary analysis. An overview of the study design is presented in Figure 8.

The data cutoff for the primary analysis will occur when all randomized subjects in the Randomization Phase have completed Week 24 assessments or have discontinued study treatment prior to Week 24. After the primary analysis is completed, subjects still receiving study treatment may continue taking lenvatinib and everolimus after the data cutoff for the primary analysis. Subjects will continue to receive investigational product after the data cutoff for the primary analysis until

they complete the Off-treatment visit. The definition of the **End of Study** is the last subject's last assessment (Off-Treatment Visit) after the data cutoff for the primary analysis.

The data obtained after the data cutoff for the primary analysis will be summarized and included in the CSR at the end of study as an addendum.

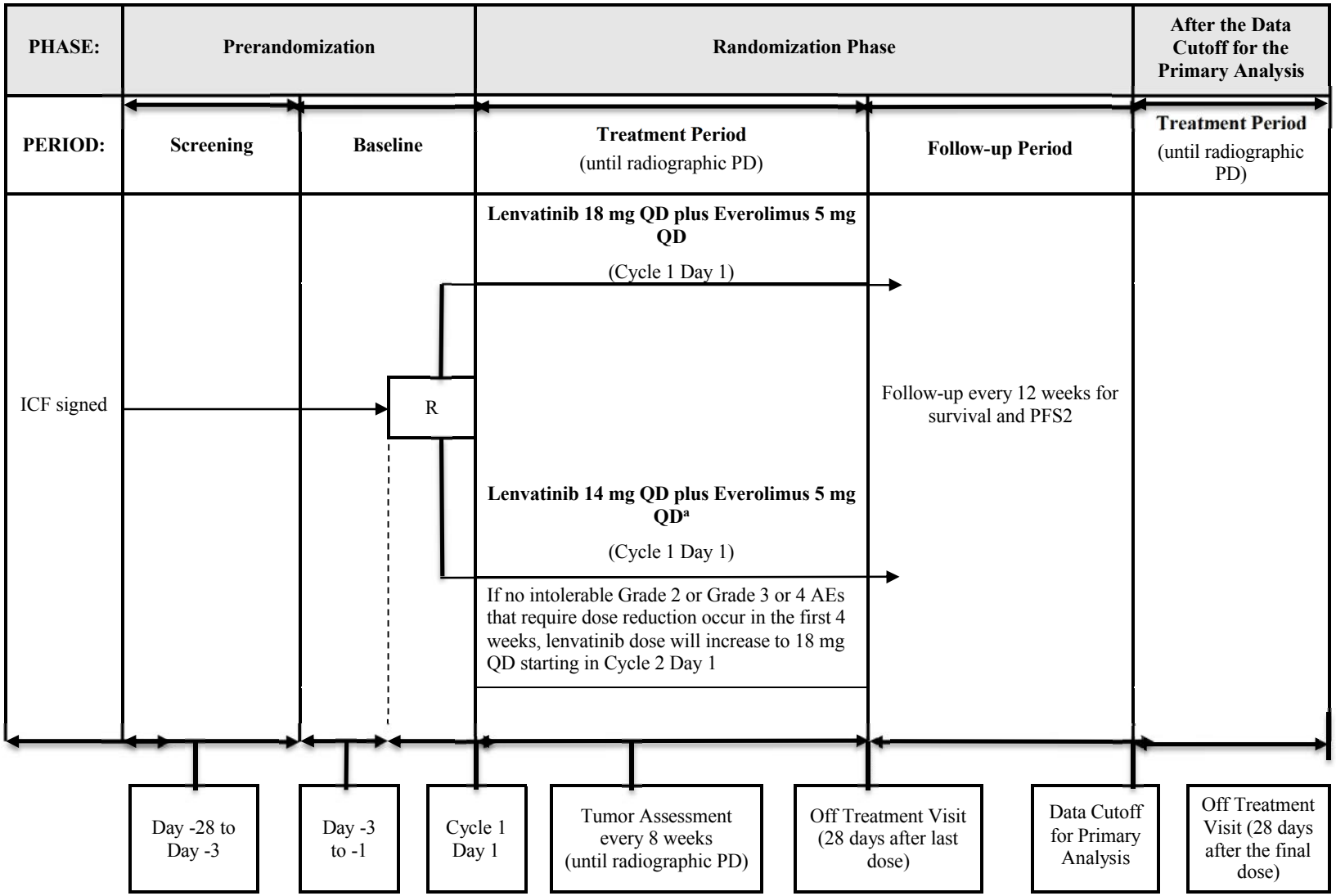

PHASE:
Prerandomization
Randomization Phase
After the Data Cutoff for the Primary Analysis
PERIOD:
Screening
Baseline
Treatment Period
(until radiographic PD)
Follow-up Period
Treatment Period
(until radiographic PD)
Lenvatinib 18 mg QD plus Everolimus 5 mg QD
(Cycle 1 Day 1)
ICF signed
R
Follow-up every 12 weeks for survival and PFS2
Lenvatinib 14 mg QD plus Everolimus 5 mg QD[a]
(Cycle 1 Day 1)
If no intolerable Grade 2 or Grade 3 or 4 AEs that require dose reduction occur in the first 4 weeks, lenvatinib dose will increase to 18 mg QD starting in Cycle 2 Day 1
Day -28 to Day -3
Day -3 to -1
Cycle 1 Day 1
Tumor Assessment every 8 weeks (until radiographic PD)
Off Treatment Visit (28 days after last dose)
Data Cutoff for Primary Analysis
Off Treatment Visit (28 days after the final dose)

Figure 8 Study Design for Study E7080-G000-218

R = randomization
PD = progressive disease
PFS2 = PFS after next line of therapy

9.1.1 Prerandomization

The Prerandomization Phase will last no longer than 28 days and will include a Screening Period to establish protocol eligibility and a Baseline Period to confirm eligibility and establish disease characteristics prior to randomization and treatment.

9.1.1.1 Screening Period

Screening will occur between Day -28 and Day -3. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility according to the inclusion and exclusion criteria listed in Sections 9.3.1 and 9.3.2, respectively. The screening assessment can serve as the baseline assessment if performed within 72 hours before randomization. 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 histological or cytological confirmed diagnosis of predominant clear cell RCC (original tissue diagnosis is acceptable) and documented evidence of advanced RCC.

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 baseline assessment can be performed from Day -3 through Day -1 or prior to randomization on Cycle 1/Day1. The screening assessment can serve as the baseline assessment if performed within 72 hours before randomization. Laboratory tests and a pregnancy test (for female subjects of childbearing potential) may be performed up to 72 hours before randomization.

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

9.1.2 Randomization Phase

The Randomization Phase will begin at the time of randomization of the first subject and will include both a Treatment Period and a Follow-Up Period. The data cut off for the primary analysis will occur at the end of the Randomization Phase, which is defined as when the last subject enrolled completes the Week-24 tumor or discontinues study treatment prior to Week 24. Subjects will be randomized in a 1:1 ratio. After the data cut off for the primary analysis, subjects who are still on study treatment will continue to receive investigational product until they complete the Off-Treatment Visit. The last subject last visit will be the date of the Off-Treatment Visit for the last subject's last assessment after the data cutoff for the primary analysis.

9.1.2.1 Treatment Period

The Treatment Period will begin with the first dose of study drug administration in Cycle 1 and continue in 28-day cycles until completion of the Off-Treatment Assessments (within 28 days after the last study drug administration). Subjects will undergo safety and efficacy assessments as defined in the Schedule of Procedures/Assessments (Table 6). Subjects will continue to receive study drug until confirmed disease progression, lost to follow-up, development of unacceptable toxicity, subject request, withdrawal of consent, or study termination by the sponsor. Subjects who discontinue treatment before the data cutoff for the primary analysis will enter the Follow-up Period and will be followed every 12 weeks (±1 week) after the Off-Treatment Visit. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.

9.1.2.2 Follow-Up Period

The Follow-Up Period will begin immediately after the off-treatment assessments have been completed and will continue as long as the study subject is alive, until the study subject withdraws consent, or until the data cutoff for the primary analysis. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessments every 8 weeks and as of Amendment 06, send these to the imaging core laboratory (ICL) until documentation of disease progression or start of another anticancer therapy. Following the Off-Treatment Visit, subjects will continue to be followed every 12 weeks (±1 week) for survival and PFS2, and all anticancer treatments received will be recorded until the data cutoff for the primary analysis. This information will be recorded unless the information is not allowed to be provided due to confidentiality.

If a subject discontinues study treatment and does not consent to continued follow-up, the investigator must not access confidential records that require the subject's consent. However, an investigator may consult public records to establish survival status. Copies of tumor assessment scans will no longer be sent to the ICL and independent review will not be carried out during the Follow-Up Period.

All subjects who are still on study treatment following the data cutoff for the primary analysis (ie, at the end of the Randomization Phase) will continue to receive the same study treatment. Tumor assessments will be performed according to the local standard of care, but not less frequently than every 12 weeks or earlier if clinically indicated, and scans will no longer be required to be sent to the ICL. Subjects will continue to receive study treatment until confirmed disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, lost to follow up or study termination by the sponsor. If the study is terminated by the sponsor, study drug (s) will be provided to subjects where commercial access is not available.

The Off-Treatment Visit will occur within 28 days after the final dose of study treatment. All AEs and SAEs will be captured up to 28 days after last dose of study drug (Table 7).

9.2 Discussion of Study Design, Including Choice of Control Groups

Originally, this was a multicenter, randomized, double-blind study, conducted as a postmarketing requirement by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Following the unblinding on 14 Jul 2018, Study 218 will be conducted in an open-label fashion; all ongoing and newly enrolled subjects, as well as investigational site personnel, will be unblinded as to the subjects' treatment assignment.

Lenvatinib 18 mg daily in combination with everolimus 5 mg daily is approved in the US and EU for the treatment of adult patients with advanced renal cell carcinoma (RCC) following 1 prior VEGF-targeted therapy. The safety and efficacy of lenvatinib and everolimus in combination was investigated in Study E7080-G000-205 (hereafter referred to as "Study 205") in subjects with predominant clear-cell RCC following 1 prior VEGF-targeted treatment. The combination significantly prolonged PFS compared with either agent as monotherapy, and the safety profile for the combination treatment was consistent with the known toxicities of each individual agent, with no unexpected TEAEs observed. Grade 3 and Grade 4 AEs occurred in 36/51 (71%) of the subjects in the lenvatinib plus everolimus cohort.

The intent of the current 2-arm study is to determine whether a different dosing regimen for lenvatinib in combination with everolimus can maintain the significant efficacy (ORR_{24W}) while reducing the frequency of Grade 3 and Grade 4 AEs. To that end, Eisai and the FDA have collaboratively developed a tumor-growth inhibition model that incorporates tumor suppression by both lenvatinib and everolimus and tumor resistance to lenvatinib for the purpose of evaluating safety and efficacy. Eisai and the FDA both utilized this model to explore various exposure-response analyses for the time course of tumor burden (size) and dose-altering AEs with data from Study 205. The modeling results showed that daily starting doses of lenvatinib 14 mg or lenvatinib 18 mg in combination with everolimus 5 mg were indicated. The reference 18-mg lenvatinib dose regimen will only allow reduction of the dose as necessary to control AEs. In contrast, the 14-mg lenvatinib dose regimen will require one 4 mg/day increase in the dose on Day 1 of Cycle 2, if the subject is tolerating the dose (while also allowing reduction of the dose whenever necessary to control AEs).

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups.

9.3 Selection of Study Population

Approximately 338 subjects will be randomized (169 subjects in each treatment arm) at approximately 100 sites worldwide. 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. Histological or cytological confirmation of predominant clear cell RCC (original tissue diagnosis of RCC is acceptable).
2. Documented evidence of advanced RCC.
3. One prior disease progression episode on or after vascular endothelial growth factor (VEGF)-targeted treatment (for example, but not limited to, sunitinib, sorafenib, pazopanib, cabozantinib, bevacizumab, axitinib, vatalanib, AV951/ tivozanib) administered for the treatment of RCC. Prior PD-1/PD-L1 treatment in addition to 1 prior VEGF-targeted treatment is allowed.
4. At least 1 measurable target lesion according to RECIST 1.1 meeting the following criteria:
   - Lymph node (LN) lesion that measures at least 1 dimension as ≥1.5 cm in the short axis
   - Non-nodal lesion that measures ≥1.0 cm in the longest diameter
   - The lesion is suitable for repeat measurement using computerized tomography/magnetic resonance imaging (CT/MRI). Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of disease progression based on RECIST 1.1 to be deemed a target lesion.
5. Male or female subjects age ≥18 years (or any age >18 years if that age is considered to be an adult per the local jurisdiction) at the time of informed consent.
6. Karnofsky Performance Status (KPS) of ≥70.
7. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week before the Cycle 1/Day 1.
8. Adequate renal function defined as calculated creatinine clearance ≥30 mL/min per the Cockcroft and Gault formula (Appendix 1).
9. Adequate bone marrow function defined by:
   - Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5 x 10^9/L)
   - Platelets ≥100,000/mm^3(≥100 x 10^9/L)
   - Hemoglobin ≥9 g/dL
10. Adequate blood coagulation function defined by International Normalized ratio (INR) ≤1.5 (except for subjects on warfarin therapy where INR must be ≤3.0 prior to randomization).
11. Adequate liver function defined by:
    - Total bilirubin ≤1.5 x ULN except for unconjugated hyperbilirubinemia of Gilbert's syndrome
    - Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN) Subjects with bone metastases with ALP values greater than 3 times can be included.
12. Subject must voluntarily agree to provide written informed consent.
13. Subject must be willing and able 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. More than 1 prior VEGF-targeted treatment for advanced RCC.
2. Subjects with Central Nervous System (CNS) metastases are not eligible, unless they have completed local therapy for at least 4 weeks and have discontinued the use of corticosteroids for this indication or are on a tapering regimen of corticosteroids (defined as ≤10 mg prednisolone equivalent) before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
3. Active malignancy (except for RCC or definitively treated basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within the past 24 months.
4. Any anti-cancer treatment (except for radiation therapy, see exclusion #5) within 21 days or any investigational agent within 30 days prior to the first dose of study drug; subjects should have recovered from any toxicity related to previous anti-cancer treatment to Common Terminology Criteria (CTC) grade 0 or 1.
5. Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start.
6. Known intolerance to study drug (or any of the excipients) and/or known hypersensitivity to rapamycins (eg, sirolimus, everolimus, temsirolimus) or any of the excipients.
7. Subjects with proteinuria >1+ on urinalysis will undergo 24-h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24 h will be ineligible.
8. Fasting total cholesterol >300 mg/dL (or >7.75 mmol/L) and/or fasting triglycerides level >2.5 x 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: these subjects can be included after initiation or adjustment of glucose-lowering medication.
10. Prolongation of QTc interval to >480 ms.
11. Subjects who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.
12. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib or everolimus.
13. Bleeding or thrombotic disorders, or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (eg, carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
14. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

15. Significant cardiovascular impairment within 6 months of the first dose of study drug; history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke, cardiac arrhythmia associated with significant cardiovascular impairment, or left ventricular ejection fraction (LVEF) below the institutional normal range as determined by screening multigated acquisition (MUGA) scan or echocardiogram.
16. Active infection (any infection requiring systemic treatment).
17. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
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:
    - do not agree to use a highly effective method of contraception for the entire study period and for up to 8 weeks after study drug discontinuation, ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or hormone releasing system (IUS
        - a contraceptive implant
        - an oral contraceptive** (with additional barrier method)

OR

- do not have a vasectomized partner with confirmed azoospermia.

For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTES:

*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).

Must be on a stable dose of the **same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug and for the duration of the study.

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 other 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 PFS2 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 PFS2 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 Discontinuation from Treatment CRF page will be completed indicating the primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from treatment. 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 without progression should have disease assessments every 8 weeks (±1 week) from the date of the last assessment until disease progression is documented, another anticancer therapy is initiated or the data cutoff for the primary analysis.

All subjects will be followed for PFS2 and survival until death, except where a subject withdraws consent or until the data cutoff for the primary analysis.

9.4 Treatments

9.4.1 Treatments Administered

Study subjects and investigator site personnel are unblinded as to lenvatinib treatment assignment. Lenvatinib will be administered as 3 capsules daily. These 3 capsules will consist of 10-mg and 4-mg capsules of lenvatinib or matching placebos provided in the appropriate configuration based on the subject's assigned dose. Investigators will provide the lenvatinib pack containing the prescribed dose and the subject will take all capsules, including any placebo. The sponsor may substitute drug supply without placebo capsules when resupplying study drug. In addition, the sponsor may make changes to the packaging of lenvatininb clinical supplies at its discretion. Changes may include the use of child-resistant bottles rather than child-resistant wallets. Child-resistant bottles will not include placebo. If changes to packaging is required, appropriate communication will be provided to the investigator at the study sites. Everolimus will be provided by the sponsor as 5-mg tablets, packaged in blisters.

Table 1. Study Treatments

Total Dose (QD)	Capsule Allocation			
	10 mg Lenvatinib	10 mg Placebo	4 mg Lenvatinib	4 mg Placebo
18 mg	1	0	2	0
14 mg	1	0	1	1
10 mg	1	0	0	2
8 mg	0	1	2	0
4 mg	0	1	1	1

QD = once daily.
All subjects also receive one 5-mg dose of everolimus QD.
N.B For subjects transferred to child-resistant bottles, placebo will not be provided

Lenvatinib 14 mg or 18 mg once daily plus everolimus 5 mg once daily will be taken orally in each 28-day cycle during the Randomization Phase and in 56-day cycles after the data cutoff for the primary analysis. Study drug should be taken at approximately the same time each morning. Study drug may be taken in a fasting state or following a meal.

Lenvatinib doses will be packaged in child-resistant wallets in a combination of active 4-mg and 10-mg capsules and/or matching placebo totaling 18 mg or 14 mg (or 10 mg, 8 mg, or 4 mg, depending on the assigned starting dose, and in the event the investigator decides that dose reduction is needed for treatment-related toxicity). The sponsor may substitute drug supplies without placebo capsules when resupplying study drug. The sponsor may also change the packaging of lenvatininb from child-resistant wallets to child-resistant bottles. Child-resistant bottles will not include placebo.

Dose Up-Titrations (14-mg Arm Only)

For subjects in the 14-mg QD (+everolimus 5 mg) arm, if there are no intolerable Grade 2 or any ≥ Grade 3 TEAEs that require dose reduction in the first 28-day cycle (ie, the first 4 weeks of treatment), lenvatinib dose will be escalated to 18 mg QD (+everolimus 5 mg). See the Interactive Voice and Web Response System (IxRS) Manual and revised Pharmacy Manual for further instructions.

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

Dose reductions for toxicity may be instituted at any time as necessary.

Adverse events will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Dose reduction and interruptions for subjects who experience lenvatinib-everolimus combination therapy-related toxicity (except hypertension and non-infectious pneumonitis)

will be managed as described in Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity." For treatment-related hypertension and non-infectious pneumonitis, refer to Management of Hypertension (Section 9.4.2.2) and Management of Non-infectious Pneumonitis (Section 9.4.2.5) for dose modification guidelines. Investigators will decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs is required.

Lenvatinib dose reductions will occur in succession based on the previous dose level. The lenvatinib and everolimus dose may not be increased at a later date, unless the dose was mistakenly decreased; in this situation, the sponsor's approval is required to increase the dose. Subjects in either arm will be allowed a maximum of 3 lenvatinib dose reductions for lenvatinib-related toxicity.

Refer to the subsections below for management of proteinuria (Section 9.4.2.3), diarrhea (Section 9.4.2.4), infections (Section 9.4.2.6), blood glucose/lipids (Section 9.4.2.7), hepatotoxicity (Section 9.4.2.8), thromboembolic events (Section 9.4.2.9), posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS) (Section 9.4.2.10), and hypocalcemia (Section 9.4.2.11), as appropriate, in addition to consulting the dose modification table (Table 2).

Table 2 Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d,e] or Grade 3[f]		
First occurrence	Interrupt lenvatinib and everolimus until resolved to Grade 0 - 1 or tolerable Grade 2	Reduce lenvatinib dose 1 level and resume everolimus at the same dose as prior to dose interruption[b]
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved to Grade 0 – 1 or tolerable Grade 2	Reduce lenvatinib dose 1 level. Dose reduction of everolimus to 5 mg every other day may be considered for Grade 3 toxicity[e]
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved to Grade 0 - 1 or tolerable Grade 2	Reduce lenvatinib dose 1 level. Dose reduction of everolimus for Grade 3 toxicity may be considered as follows:[e] 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

Table 2 Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity

Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus	Discontinue study treatment
Grade 4[g]: Discontinue Study Treatment		

For grading, see Common Terminology Criteria for Adverse Events (CTCAE v4.03. (Appendix 3). Collect all CTC grades of AEs, decreasing and increasing grade.

a: Interruption of study treatment for more than 28 days (due to treatment-related toxicities) will require Sponsor's approval before treatment can be resumed.

b: Initiate optimal medical management for nausea, vomiting, hypothyroidism, hypertension and/or diarrhea before any study treatment interruption or dose reduction. For treatment-related hypertension and non-infectious pneumonitis, refer to Management of Hypertension (Section 9.4.2.2) and Management of Non-infectious Pneumonitis (Section 9.4.2.5) for dose modification guidelines.

c: Applicable only to those Grade 2 toxicities judged by the subject and/or physician to be intolerable.

d: Obese subjects with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1 weight loss). These subjects will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal body mass index (BMI) (if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.

e: For Grade 2 toxicity, resume everolimus at the same dose as prior to dose interruption. For Grade 3 toxicity, investigator 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.

f: For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with the Sponsor.

g: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

9.4.2.1 Dose Reduction Schedule for Intolerable Toxicities

Lenvatinib dose reductions occur in succession based on the previous level (18, 14, 10, 8, and 4 mg/day) as shown in the table below:

Table 3 Dose Reductions for Lenvatinib in Combination With 5 mg Everolimus

Current Dose (QD)	Dose Reduction[a]
18 mg	14 mg QD
14 mg	10 mg QD
10 mg	8 mg QD
8 mg	4 mg QD
a: Subjects in either arm will be allowed a maximum of 3 lenvatinib dose reductions for lenvatinib-related toxicity.	

Note: Subjects in either arm will be allowed a maximum of 3 lenvatinib dose reductions for lenvatinib-related toxicity.

At every dose change, the investigator or a designee will call the Interactive Voice and Web Response System (IxRS) to register the subject's visit (see the IxRS Manual for further instructions). At each of these postrandomization visits, the investigator will select the subject's appropriate treatment dose in accordance with the protocol. As of 01 Oct 2020, the IxRS will be discontinued. Refer to the revised Pharmacy Manual for complete instructions.

9.4.2.2 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP of ≤150/90 mmHg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) is confirmed on 2 assessments a minimum of 30 minutes apart. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. After the data cutoff for the primary analysis, one BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, appropriate antihypertensive therapy should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is first observed on 2 assessments a minimum of 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib 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 ≥160/100 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the subject has been on the same hypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

During the Treatment Period, subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 or more frequently as clinically indicated until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 1 treatment cycle (ie, 56-day cycle). If a repeat 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 1 treatment cycle (ie, 56-day cycle).

The following guidelines should be followed for the management of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg confirmed on repeat measurements after 30 minutes:

1. Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving this.

2. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added.
3. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted. It should be restarted at 1 dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at an additional dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at a third dose reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
   - 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):

1. Institute appropriate medical management
2. Discontinue study treatment

9.4.2.3 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments (Table 6) and the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). Guidelines for assessment and management of proteinuria:

1. Grading will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to instructions contained in Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity,"
2. A 24-hour urine collection (within 72 hours) to verify the grade of proteinuria for protein quantitation is required in the following situations:
   - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug

- A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
- When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is 2+, 3+, or 4+

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+ or negative for 1 treatment cycle (ie, 56-day cycle).

9.4.2.4 Management of Diarrhea

An antidiarrheal agent should be recommended to the subject at the start of study treatment and subjects should be instructed and educated to initiate antidiarrheal treatment at the first onset of soft bowel movements. The choice of antidiarrheal agent should be individualized to the subject's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity," should be followed.

9.4.2.5 Management of Non-Infectious Pneumonitis

Non-infectious pneumonitis is a recognized class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis was described in 19% of subjects taking everolimus (AFINITOR® Package Insert). Some cases were severe and on rare occasions, a fatal outcome was observed. Investigators should therefore consider a diagnosis of non-infectious pneumonitis in subjects presenting with non-specific respiratory signs and symptoms and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations.

Subjects who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms (CTCAE Grade 1) may continue study dosing without dose adjustments.

- If symptoms are moderate (CTCAE Grade 2):
  - Lenvatinib-everolimus combination therapy should be interrupted and the use of corticosteroids may be indicated until symptoms abate (resolved to CTCAE Grade 0-1) and may then be restarted at the same doses prior to study treatment interruption.
  - If Grade 2 non-infectious 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).
- If symptoms are severe (CTCAE Grade 3):
  - Lenvatinib-everolimus combination therapy should be interrupted and the use of corticosteroids may be indicated until clinical symptoms resolve (to CTCAE

Grade 0-1). Investigators will decide the probability of the event being related to 1 or both drugs as to whether dose modification of 1 or both drugs is required.

- If symptoms are life-threatening (CTCAE Grade 4):
  - Everolimus should be discontinued. Investigators will decide the probability of the event being related to 1 or both drugs as to whether discontinuation of 1 or both drugs is required.

9.4.2.6 Management of Infections

Everolimus has immunosuppressive properties and may predispose subjects to infections. Therefore, it is important to monitor for signs and symptoms of infection, and treat promptly. Dose alterations of everolimus may be required in accordance with prescribing information.

9.4.2.7 Management of Blood Glucose and Lipids

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

Blood glucose will be monitored as specified in the Schedule of Procedures/Assessments. For subjects with blood glucose > ULN, a fasting (>6 h, water only) blood glucose sample will be obtained. Grading according to CTCAE v4.03 will be based on the fasting blood glucose result. The choice of hypoglycemic agent should be individualized to the subject's clinical circumstances and follow standard medical practice.

Dose alterations of everolimus may be required in accordance with prescribing information.

9.4.2.8 Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be monitored at baseline, every 2 weeks for the first 2 months, and monthly thereafter, and as clinically indicated (see Schedule of Procedures/Assessments, Table 6) and the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). If signs/symptoms indicating liver injury occur, instructions contained in Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity," should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

9.4.2.9 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, and deep-vein thrombosis (DVT) signs 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

Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity," should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

9.4.2.10 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS) were reported for less than 1% of lenvatinib-treated subjects. PRES/RPLS is a neurological disorder that 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/RPLS. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES/RPLS, instructions contained in Table 2, "Dose Modification Guidelines for Lenvatinib-Everolimus Combination Treatment-Related Toxicity," should be followed.

9.4.2.11 Management of Hypocalcemia

Serum calcium should be monitored per the Schedule of Procedures/Assessments. Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v4.03, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] x 0.8 + serum calcium)

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

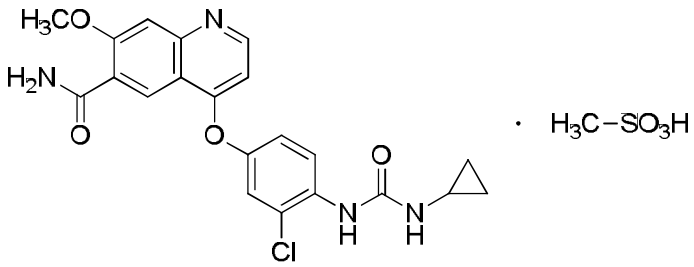
9.4.3 Identity of Investigational Products

The study drug under evaluation in this study is lenvatinib 14 mg and 18 mg in combination with everolimus 5 mg. Lenvatinib will be packaged in a double-blind configuration (until the current supply is exhausted) and will be supplied as 4-mg and 10-mg capsules (and matching placebo) by the sponsor. The sponsor may substitute drug supply without placebo capsules when resupplying study drug. In addition, the sponsor may make changes to the packaging of lenvatininb at its discretion. Changes may include the use of child-resistant bottles rather than child-resistant wallets. Child-resistant bottles will not include placebo. Lenvatinib is formulated with calcium carbonate, d-mannitol, microcrystalline cellulose,

hydroxypropylcellulose, low-substituted hydroxypropylcellulose, and talc. Everolimus will be supplied by the sponsor as 5-mg tablets, packaged in blisters.

9.4.3.1 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:



9.4.3.2 Comparator Drug

Not applicable.

9.4.3.3 Labeling for Study Drug

Lenvatinib, identical placebo, 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 provided (but not limited to):

- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Unique package number
- Storage conditions, expiration date if necessary

9.4.3.4 Storage Conditions

Study drugs 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 if regionally required, the head of the medical institution) 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.

9.4.4 Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomly assigned to each treatment arm in a 1:1 ratio. Randomization will follow a predefined randomization scheme based on the following stratification factors: MSKCC prognostic groups (favorable, intermediate, and poor risk); and whether subjects have had a prior PD-1/PD-L1 treatment (yes and no).

The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

Randomization will be performed centrally by an Interactive Voice and Web Response System (IxRS). At enrollment (and after successful completion of Visit 1), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique 6-digit randomization number.

At every subsequent dose change, the investigator or a designee will call the IxRS to register the subject's visit (see the IxRS Manual for further instructions). At each of these postrandomization visits, the investigator will select the subject's appropriate treatment dose in accordance with the protocol. As of 01 Oct 2020, the IxRS will be discontinued. Refer to the revised Pharmacy Manual for complete instructions.

9.4.5 Selection of Doses in the Study

In subjects with advanced predominant clear RCC following 1 prior VEGF-targeted treatment, the current approved dose is 18 mg lenvatinib in combination with 5 mg everolimus. Study 205 demonstrated that the combination significantly prolonged PFS compared with either agent as monotherapy.

The intent of the current study is to determine whether an alternate dosing regimen can provide comparable efficacy (based on ORR_{24WK}) with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg (based on treatment-emergent intolerable Grade 2 or any ≥ Grade 3 AEs in the first 24 weeks after randomization). A tumor-growth model that was developed collaboratively by Eisai and the FDA was used to explore various exposure-response analyses for the time course of tumor burden (size) and dose-altering AEs with data from Study 205. The modeling results showed that lenvatinib daily doses less than 18 mg were less effective, ie, the simulated percent reduction in tumor size was less and occurred later than with the 18-mg dose. Further, the modeling results showed that efficacy regimens that utilize lower starting doses (ie, 12 mg or 14 mg) but allowed up-titration of doses showed equivalent or superior tumor reduction to an 18-mg starting dose that allowed only dose reduction of lenvatinib. The utility of an up-titration to

22 mg was also modeled; there was no added benefit to increasing the dose to 22 mg from the 14-mg starting dose.

Based on these simulations, daily starting doses of lenvatinib 14 mg or 18 mg in combination with everolimus 5 mg were chosen. The reference 18-mg lenvatinib dose regimen will only allow reduction of the dose as needed to control AEs. The 14-mg lenvatinib dose regimen will require one 4-mg per day increase in the dose on Day 1 of Cycle 2, if the subject tolerates the dose).

9.4.6 Selection and Timing of Dose for Each Subject

Lenvatinib will be administered as 3 capsules daily. These 3 capsules will consist of 10-mg and 4-mg capsules of lenvatinib or matching placebos provided in the appropriate configuration based on their assigned dose (18 mg or 14 mg). Everolimus is provided as 5-mg tablets (See Section 9.4.1, Table 1).

Study drugs are to be taken orally once a day continuously from Day 1/Cycle 1 onward at approximately the same time in the morning without regard to food intake. A cycle is considered 28 days during the Randomization Phase and 56 days after the data cutoff for the primary analysis. 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 drug 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.

9.4.7 Blinding

As of 14 Jul 2018, the study is no longer blinded.

9.4.8 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 evaluation of or interact with lenvatinib 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) lenvatinib.

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. Granulocyte colony-stimulating factor (g-CSF) 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.

9.4.8.1 Drug-Drug Interactions

Lenvatinib's weak in vitro inhibitory and induction potential on cytochrome P450 (CYP P450) enzymes (Study No. XT063020) suggests a low risk of lenvatinib interference with the PK of other drugs metabolized by CYP P450 enzymes that are co-administered in usual clinic practice. Nonclinical studies identify CYP3A4 as the important CYP isozyme responsible for human hepatic metabolism of lenvatinib. However, clinical studies conducted showed that co-administration of lenvatinib with CYP3A4/P-glycoprotein (P-gp) inhibitors or inducers is not of clinical concern. The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (LENVIMA® Package Insert). Please refer to Appendix 2 and http://medicine.iupui.edu/clinpharm/ddis/ for the most current information.

For subjects receiving everolimus, drugs or substances (including herbal supplements or grapefruit juice) known to be potent inhibitors of CYP3A4/P-gp should not be used. Potent inducers of CYP3A4/P-gp should not be used unless there is no alternative treatment available. Moderate/ weak inhibitors or inducers or substrates of CYP3A4 and/or P-gp should be used with caution. Dose reduction of everolimus may be considered when co-administering moderate CYP3A4 or P-gp inhibitors. For further information please refer to the prescribing information.

9.4.8.2 Prohibited Concomitant Therapies and Drugs

Prior therapy must be documented by the following criteria prior to entry into study:

- Any single agent therapy, and any combination of cytotoxic, hormonal, biological targeted agents, and/or humanized antibodies, scheduled to be administered as a preplanned treatment, given concomitantly, sequentially or both, is considered 1 regimen.
- Planned neoadjuvant chemotherapy (to debulk the tumor prior to surgical intervention) plus postoperative adjuvant chemotherapy is considered 1 regimen.
- For chemotherapy: if, due to toxicity, the dosing of one or more of the components must be reduced, or one or more of the components of the regimen must be omitted, or one of the components must be replaced with another similar drug, the changed version of the original regimen is not considered a new regimen. However, if a new component, dissimilar to any of the original components, is added to the regimen, the new combination is considered a new regimen.
- For prior VEGF/VEGFR-targeted agents, treatment with each agent will be counted individually, regardless of the duration of administration.
- If the treatment is interrupted for surgery or radiotherapy or any other reason and then continues with an unchanged schedule and components, that treatment is considered as 1 regimen despite the interruption.

Subjects should not receive other antitumor therapies or other investigational drugs while on study. If subjects receive additional antitumor therapies, such as chemotherapy, tyrosine kinase inhibitors (TKIs), hormone therapy, radiotherapy (except for palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases), antitumor interventions (surgical resection, thoracentesis, etc), or immunotherapy, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These subjects should complete all off-treatment assessments and continue to be followed for survival in the Follow-Up Period until death, except where a subject withdraws consent or until the data cutoff for the primary analysis (ie, follow-up ends at the end of the Randomization Phase), or to complete all off-treatment assessments after the data cutoff for the primary analysis.

Live vaccines while participating in the study are prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg. Flu-Mist®) are live attenuated vaccines and are not allowed.

For further information on the prohibited concomitant therapies for everolimus, please refer to the respective Prescribing Information.

Treatment (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs, etc.) of complications of AEs or therapy to ameliorate symptoms may be administered at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study medication. For clarification, the following concomitant therapies are also allowed:

- Adjuvant hormonal therapy for history of definitively treated breast or prostate cancer
- Bisphosphonates or denosumab
- Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases will be permitted without being considered progressive disease

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

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding

Any additional procedural or patient specific particularities should be discussed with the sponsor.

9.4.9 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study, including the Follow-up Period. Clinical Research Associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.10 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) 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 or Investigator and Site Information Form, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all sub-investigators listed on Form FDA 1572 or Investigator and Site Information Form, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license (required in the US) 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 (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (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 to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

Unused study drugs must be returned to the clinic by the subject in the original packaging. The site must maintain an accurate and timely record of the following: receipt of all study

drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to:
(a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs 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 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 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 Health Regulatory Agency [MHRA]). As applicable, all unused study drugs and empty and partially empty blister packages, wallets or bottles from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs 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 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 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 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 may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs 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 and Baseline Assessments

Subject demography and baseline characteristics will be collected during the Prerandomization Phase. Demography information includes date of birth (or age), sex, and race/ethnicity (recorded in accordance with prevailing regulations). Baseline characteristics will include Karnofsky Performance Status (KPS) (Appendix 4), NYHA cardiac disease classification (Appendix 5), MSKCC prognostic group (Appendix 6), and RCC American Joint Committee on Cancer (AJCC) staging at the time of diagnosis (Appendix 7).

Medical and surgical histories will be obtained during the Prerandomization Phase, along with a record of prior and concomitant medications.

Physical examinations (comprehensive or symptom-directed) will be performed as specified in the Schedule of Procedures/Assessments (Table 6) and the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). 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 investigational site. Significant findings prior to the start of study drug 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 1.1 as defined in Inclusion Criterion #4 (Appendix 8). 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

Tumor assessments will be performed using RECIST 1.1 (Appendix 8). Investigator-determined response assessments will be performed at each assessment time point and entered onto the case report form (CRF). Copies of all tumor assessment scans will be sent to an ICL designated by the sponsor for blinded independent efficacy assessment until the data cutoff for the primary analysis. For subjects enrolled after implementation of Amendment 06, tumor assessments will be carried out following the guidelines provided by the ICL.

Tumor assessments (computed tomography [CT] chest, and CT or MRI abdomen, pelvis, and other known or suspected sites of disease) will be performed during the Prerandomization Phase and then, during the Randomization Phase, every 8 weeks (within the 8th week) until documentation of progressive disease as determined by the investigator and on a schedule as determined by the treating physician after the data cutoff for the primary analysis, but not less frequently than every 12 weeks or earlier if clinically indicated. Historical CT or MRI scans performed within 28 days of randomization but before informed consent may be used as screening scans provided they meet minimum standards as separately defined by the ICL. The same imaging modality and image-acquisition protocol (including use or nonuse of contrast) should be used consistently across all time points. All responses must be confirmed no less than 4 weeks following the initial indication of response. A chest x-ray or a skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

A bone scan (^{99}m-technetium-based scintigraphy, whole-body bone MRI, or ^{18}F-sodium fluoride positron emission tomography [NaF PET]) will be performed during the Prerandomization Phase to establish a baseline (a historical bone scan performed within 6 weeks prior to randomization is acceptable), every 24 weeks after randomization, within a

target of 1 week but no more than 2 weeks following a complete response (CR) as assessed by the investigator, and as clinically indicated after the data cutoff for the primary analysis. Lesions identified on bone scans should be followed at all tumor assessment time points with cross-sectional imaging.

A brain scan will be performed at screening and as clinically indicated thereafter, and within a target of 1 week but no more than 2 weeks following achievement of a confirmed CR. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all protocol-specified tumor assessment time points (eg, every 8 weeks). Subjects with protocol-eligible treated brain metastases should also have brain CT/MRI performed as per local standard of care. For other subjects, brain scans should be performed as clinically indicated.

Stable disease must be achieved at ≥7 weeks after randomization to be considered best overall response. Subjects going off treatment without disease progression in the Treatment Period will continue to undergo tumor assessments in the Follow-up Period per the above schedule until disease progression is documented, another anticancer therapy is initiated, or data cutoff for the primary analysis.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Sparse PK samples (plasma for lenvatinib and whole blood for everolimus) will be collected from all subjects and will be analyzed using a population PK approach (PopPK). The timing for obtaining the 7 PK sampling time points (one tube each for lenvatinib and everolimus PK) is shown in the Schedule of Procedures/Assessments (Table 6) and Table 4. See the Laboratory Manual for a description of collection, handling, and shipping procedures for PK samples. A separate statistical analysis plan will be developed for the PopPK analysis.

Table 4 Pharmacokinetic Sampling Time Points

Time Point	Sample Number	Time (h)
Cycle 1/Day 1	1	0.5-4 h postdose
	2	6-10 h postdose
Cycle 1/Day 15[a]	3	Predose on Day 15 (Cycle 1)
	4	0.5-4 h postdose
	5	6-10 h postdose
Cycle 2 Day 1	6	Predose on Day 1 (Cycle 2)
	7	2-12 h postdose

h = hour(s).
a If dose interruption is necessary in these time points, only predose sample should be collected.

9.5.1.3.2 PHARMACODYNAMIC AND OTHER BIOMARKER ASSESSMENTS

Pharmacodynamic and Other Biomarker Assessments

Blood samples will be collected for peripheral blood mononuclear cell (PBMC) and plasma isolation from all study subjects at protocol specified time points, during the Randomization Phase of the study, as indicated in the Schedule of Procedures/Assessments (Table 6). There will be no further biomarker sample collection after the data cutoff for the primary analysis. Biomarker discovery or validation will be performed to identify blood biomarkers that may be useful to measure subject response to study drug, to understand the underlying disease biology, to provide further insight into the mechanism of action of the study drug as well as for potential use in diagnostic development.

These samples may undergo enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay and/or other appropriate analysis procedures to explore blood biomarkers (eg, VEGF, Ang-2). In addition, other pharmacodynamics target engagement and response biomarkers related to study drug may be assessed. See Appendix 12 for description of sample collection and handling, procedures for securing and retention of samples, and subject privacy information).

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual (see also Appendix 12).

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE v4.03 grades (for both increasing and decreasing severity) and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and electrocardiograms (ECGs); and performance of physical examinations during the Randomization Phase. An echocardiogram or a MUGA scan including LVEF will be performed at screening, and as clinically indicated. After the data cutoff for the primary analysis, all AEs leading to study discontinuation, SAEs and concomitant medications will be monitored and recorded. Hematology and blood chemistry will be monitored prior to administration of study drug and as clinically indicated. Urine dipstick testing will be monitored at each visit and as clinically indicated. A serum or urine pregnancy test will be performed during the study for women of childbearing potential. A symptom-directed physical examination and vital signs (resting BP, HR, RR and body temperature) will be performed at each visit and as clinically indicated. A 12-lead ECG and Echocardiogram/MUCA scan will be performed as clinically indicated (Table 7).

Progression of RCC and signs and symptoms clearly related to the progression of RCC 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.

9.5.1.4.1 Adverse Events and Events Associated with Special Situations

An 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. 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. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. All AEs and SAEs will be collected for 28 days after the last dose.

After the data cutoff for the primary analysis, all AEs leading to study drug discontinuation and SAEs will be recorded until 28 days after the last dose of study drug. SAEs, irrespective of relationship to study drug, must be reported as soon as possible but not later than 24 hours from the date when the investigator becomes aware of the event.

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 (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc 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. Subjects with onset of an AE or deterioration of a preexisting AE will be followed until resolution to baseline, start of a new anticancer treatment, or death. 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 CTCAE v4.03 (Appendix 3). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity). For Grade 2 AEs that lead to changes in study drug administration (dose held, dose reduced, or dosing discontinuation), the investigator will be required to confirm in the CRF that the AE is considered intolerable.

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 non-study 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.

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

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution. A blood sample to measure study drug plasma concentrations will no longer be needed after the data cutoff for the primary analysis.

9.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urine dipstick testing, and a serum or urine pregnancy test (for female subjects of childbearing potential), are summarized in Table 5. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 6) and the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7) shows the visits and time points at which blood for clinical laboratory tests and urine for dipstick testing (and possible 24-hour urine collection to quantify the 24-hour urine protein excretion) will be collected in the study.

Clinical laboratory tests during the Randomization Phase of the study will be performed by a central laboratory. All blood and urine samples (except urine sample for urine dipstick) will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern or to guide clinical dosing, a local laboratory may be used in addition to the central laboratory testing. If central laboratory results are not available within the necessary timeframe to allow the subject to be enrolled, 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. After the data cutoff for the primary analysis, clinical laboratory tests can be performed by the local laboratory and samples will no longer be sent to the central laboratory.

Urine dipstick testing will be performed, preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site).

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with automated differential (including absolute neutrophil count and absolute lymphocyte count) INR[a]
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, magnesium, phosphorous, 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[b]	Thyroid stimulating hormone, free T4 level
Other	Albumin, cholesterol, glucose[c], lactate dehydrogenase, total protein, triglycerides, amylase, lipase, creatine kinase Serum or urine pregnancy test[d] (β-hCG or hCG)
Urine Dipstick Testing[e]	glucose, hemoglobin (or blood), ketones, pH, protein[f], specific gravity

Category	Parameters

RBC = red blood cell, WBC = white blood cell, INR = International Normalized Ratio.

a. INR should only be performed as part of the screening assessment and when clinically indicated.

b. Free T4 and TSH levels will be performed at the Screening Visit, at the Baseline Visit (or within 72 hours prior to the first dose of study drug). TSH levels will be repeated at Day 1 of every other cycle (starting with Cycle 2) and at the Off-Treatment visit.

c. For subjects with blood glucose >ULN, a fasting (>6 h, water only) blood glucose sample will be obtained.

d. For women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months)

e. If urine dipstick testing suggests a urinary tract infection, a urinalysis with microscopy and/or urine culture with sensitivities should be considered, if clinically indicated, at the institution's laboratory.

f. If urine protein by dipstick is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection should be done to quantify the 24-hour urine protein excretion.

All hematology, clinical chemistry (including pregnancy test, as applicable), and urine samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of Cycle 1, and within 48 hours of Day 1 in each treatment cycle and within 72 hours of Day 1 after the data cutoff for the primary analysis. Refer to Table 2 for 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 BP [mmHg], pulse [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 6) by a validated method. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. After the data cutoff for the primary analysis, one BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart.

Vital sign measurements (resting BP [including date and time of measurement], HR, RR and body temperature) will be obtained, excluding weight at the visits designated in the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7).

For subjects with an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mmHg), confirmation should be obtained by performing 2 assessments a minimum of 30 minutes apart.

Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 1 and Day 15 or more frequently, as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 1 treatment cycle (ie, 56-day cycle). A diary will be provided to the subject to capture the BP evaluations between study visits. See subsection for management of hypertensive subjects (Section 9.4.2.2).

9.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 6) and in the Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7). 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. A symptom-directed physical examination will be performed as clinically indicated.

9.5.1.4.6 ELECTROCARDIOGRAMS

ECGs will be performed during screening and every 4 weeks on Day 1 of each cycle during the Randomization Phase beginning with Cycle 2 and at the Off-Treatment Visit (Table 6). After the data cutoff for the primary analysis, ECGs may be performed as clinically indicated (Table 7). 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 are suggested to 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 ECHOCARDIOGRAM OR MULTIPLE GATED ACQUISITION SCAN

A MUGA scan (using technetium-^{99}m-pertechnetate) or an echocardiogram to assess LVEF will be performed at Screening and as clinically indicated (Table 6) and (Table 7). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at Baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

9.5.1.4.8 PREGNANCY TEST

A serum or urine pregnancy test (β-hCG or hCG with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG or hCG) will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than

12 months). Samples of blood or urine will be taken at designated time points as specified in the Schedule of Procedures and Assessments (Table 6) and Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7).

9.5.1.5 Other Assessments

HRQoL will be assessed at Baseline (prior to first dose of study drug), on Day 1 of each subsequent cycle, and at the Off-Treatment Visit in the Randomization Phase. HRQOL will not be assessed after the data cutoff for the primary analysis. Every effort should be made to administer HRQoL surveys prior to study drug administration and before other assessments and procedures. Subjects will complete the Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS; Appendix 9), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 (Appendix 10) and the European Quality of Life (EuroQol) EQ-5D-3L (Appendix 11) instruments.

The FKSI-DRS consists of 9 items that experts and patients have indicated are important targets for the treatment of advanced kidney cancer, and that clinical experts have indicated are primarily disease-related, as opposed to treatment-related. Symptoms assessed on the FKSI-DRS include pain, fatigue, shortness of breath, fevers, weight loss, coughing, and blood in urine. The total score can range from 0 (worst) to 36 (best).

The QLQ-C30 measure comprises 9 multiple-item scales and 6 single items. Multiple-item scales of QLQ-C30 consist of 6 functional scales (physical, role, emotional, cognitive, social and global QoL) and 3 symptom scales (fatigue, nausea and vomiting, pain). Six single-item scales of QLQ-C30 involve dyspnea, sleep disturbance, appetite loss, constipation, diarrhea and financial impact. All of the derived scales range in score from 0 to 100. For the overall HRQoL and functioning scales, a higher score is correlated with better HRQoL, whereas a higher score represents worse HRQoL for symptom scales.

The EQ-5D-3L generic QoL questionnaire is comprised of 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has 3 levels (1) no problem, (2) some problem, or (3) extreme problem. Thus, the final scoring consists of 243 possible combinations or health states. The utility value for each state is assigned on the basis of a set of preference weights (tariffs) elicited from the general population.

9.5.2 Schedule of Procedures/Assessments

Table 6 presents the schedule of procedures/assessments for the study. Table 7 presents the schedule of procedures/assessments after the data cutoff for the primary analysis.

Table 6 Schedule of Procedures/Assessments in E7080-G0000-218

Phase	**Prerandomization Phase**		**Randomization Phase All cycles are 28 days in duration**								
Period	**Screening[a]**	**Baseline[a]**	**Study Treatment Period[b]**							**Off-Tx**	**Follow- Up**
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7, 9, etc.**	**8, 10, 12, 14, etc.**		
			Cycle 1			**Cycle 2**		**Cycles 3 - Last**			
Day	**-28 to -3**	**-3 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**15**	**99**	
Procedures/Assessments											
Informed consent	X										
Medical/surgical history	X	X									
Demographic data	X										
KPS[c]	X	X				X		X			
NYHA[c]	X										
AJCC staging[d]	X										
Inclusion/exclusion	X	X									
Randomization		X									
Vital signs[e]	X	X	X		X	X	X	X	X	X	
Physical examination[f]	X	X[g]			X	X		X		X	
12-lead ECG[h]	X					X		X		X	
Echocardiogram/MUGA scan[i]	X		As clinically indicated								
Pregnancy test[j]	X	X				X		X		X	

Phase	**Prerandomization Phase**		**Randomization Phase All cycles are 28 days in duration**								
Period	**Screening[a]**	**Baseline[a]**	**Study Treatment Period[b]**							**Off-Tx**	**Follow-Up**
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7, 9, etc.**	**8, 10, 12, 14, etc.**	**99**	
			Cycle 1			**Cycle 2**		**Cycles 3 - Last**			
Day	**-28 to -3**	**-3 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**15**		
Procedures/Assessments											
Clinical chemistry/hematology[k]	X	X			X	X	X	X		X	
Urine dipstick testing[l]	X	X			X	X	X	X[l]		X	
Study drug administration			Once daily								
PK blood samples[m]			X		X	X					
Tumor assessments (CT/MRI)[n]	X		Performed every 8 weeks (counting from date of randomization), or sooner if clinically indicated, until documentation of disease progression							X	X
Bone scan[o]	X		Every 24 weeks, and as clinically indicated, and to confirm CR								
Brain scan (CT/MRI)[p]	X		X								
HRQoL[q]		X				X		X		X	
Phone contact or visit[r]				X							
Prior /Concomitant meds[S]	Throughout										Only anticancer Tx recorded during Follow-up Period
AEs/SAEs[t]	Throughout										
PFS2 and Survival[u]											X

Phase	Prerandomization Phase		Randomization Phase All cycles are 28 days in duration								
Period	**Screening[a]**	**Baseline[a]**	**Study Treatment Period[b]**							**Off-Tx**	**Follow-Up**
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7, 9, etc.**	**8, 10, 12, 14, etc.**	**99**	
			Cycle 1			**Cycle 2**		**Cycles 3 - Last**			
Day	**-28 to -3**	**-3 to -1**	**1**	**8**	**15**	**1**	**15**	**1**	**15**		
Procedures/Assessments											
Blood sample for Biomarkers[v]		X			X	X		X		X	

AEs = adverse events, BP = blood pressure, C1D1 = Cycle 1/Day 1, C1D15 = Cycle 1/Day 15, CT = computed tomography, ECG = electrocardiogram, HR = heart rate, ICL = imaging core laboratory, meds = medications, KPS = Karnofsky Performance Status, MRI = magnetic resonance imaging, MUGA = multigated acquisition, NYHA = New York Heart Association, PET = positron emission tomography, PFS2 = progression-free survival after next line of therapy, PK = pharmacokinetic, RECIST = Response Evaluation Criteria in Solid Tumors, RR = respiratory rate, SAEs = serious adverse events, Tx = treatment.

a. Subjects must be screened within 28 days prior to randomization. The screening assessment can serve as the baseline assessment, if performed within 72 hours before randomization. Baseline assessments may be performed on Day -1 or on C1D1 prior to randomization. Patients randomized after the baseline assessment must have all baseline assessments reviewed prior to C1D1. Informed consent may be obtained up to 4 weeks prior to randomization.

b. Efforts should be made to conduct study visits on the day scheduled (±3 days). The study visit (and safety assessments) still needs to occur regardless of a study medication hold per the visit schedule.

c. KPS assessment will be performed at the Screening and Baseline Visits, on C2D1, and on Day 1 of every subsequent cycle. NYHA assessment will only be performed at the Screening visit. See protocol appendices for KPS assessments and NYHA Cardiac Disease Classification.

d. TNM staging, according to AJCC criteria (Edge, et al., 2010), should be reported based on the initial diagnosis of RCC.

e. Assessments will include vital signs (resting BP [including date and time of measurement], HR, RR and body temperature), weight, and height. Height will be measured at the Screening visit only. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. An elevated BP assessment (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg should be confirmed by a repeat assessment after a minimum of 1 hour. Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 1 and 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. A diary will be provided to the subject to capture the blood pressure evaluations between study visits. See subsection for management of hypertensive subjects.
Note: During Cycle 3 and subsequent cycles, subjects may return to the clinic for the Day 15 visit if BP monitoring testing is required as specified above. The Day-15 visit is mandatory in Cycles 1 and 2.

f. A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visits, on Cycle 1/Day 15, on Day 1 of each subsequent cycle, and at the Off-Treatment assessment. A symptom-directed physical examination will be performed on C1D1

and at any time during the study, as clinically indicated.

g. Required if screening physical examination was performed >7 days prior to C1D1.
h. Single 12-lead ECG. Subjects are suggested to be in the recumbent position for a period of 5 minutes prior to obtaining ECG.
i. An echocardiogram or MUGA scan to assess LVEF will be performed at Screening and as clinically indicated.
j. A serum or urine pregnancy test will be performed at the Screening Visit, at the Baseline Visit (or within 72 hours prior to the first dose of study drug), at Day 1 of every cycle (starting with Cycle 2), and at the Off-Treatment assessment in women of childbearing potential (ie, premenopausal and perimenopausal women who have been amenorrheic for less than 12 months).
k. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 2 business days of receipt of results for all subsequent cycles. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities should be corrected in all subjects before starting treatment per the Investigator's discretion. Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified. If there is ≥Grade 3 hematologic or clinical chemistry toxicity, repeat the specific laboratory test and AE assessment at least 3-7 days (until improvement to <Grade 3). For subjects with blood glucose >ULN, a fasting (>6 h, water only) blood glucose sample will be obtained.
l. Urine dipstick testing for subjects with proteinuria ≥2+ should be performed locally every 2 weeks (on Day 1 and Day 15 or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. Urine dipstick testing should be performed preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site). If a new event of proteinuria ≥2+ occurs, the subject must resume the Day-15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months. For subjects with a history of dipstick proteinuria ≥2+, see subsection for management of proteinuria.

   Note: During Cycle 3 and subsequent cycles, subjects may return to the clinic for the Day-15 visit if urine dipstick testing is required as specified above. The Day-15 visit is mandatory in Cycles 1 and 2.
m. Blood samples for PK profiling of lenvatinib and everolimus will be drawn at 0.5-4 h and 6-10 h postdose on C1D1; predose and 0.5-4 h and 6-10 h postdose on C1D15, and predose and 2-12 h postdose on C2D1. If possible, a blood sample for the measurement of the concentration of lenvatinib should be drawn at the first report of an SAE or a severe unexpected AE. A blood sample to measure study drug plasma concentrations will no longer be needed after the data cutoff for the primary analysis.
n. **Screening:** Screening tumor assessments using contrast-enhanced CT of the chest, and contrast-enhanced CT or MRI of the abdomen and pelvis, and other areas of known or suspected disease should be performed within 28 days prior to randomization. Historical scans that were performed within this window but before informed consent may be used if consistent with imaging requirement per the ICL.

   Randomization Phase: Tumor assessments using contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis and other areas of known disease at screening or newly suspected disease should be performed every 8 weeks (during the eighth week, starting from the date of randomization), or sooner if clinically indicated, until progressive disease. For subjects enrolled after implementation of Amendment 06, detailed image acquisition guidelines will be provided by the ICL until data cut off for the primary analysis. All responses must be confirmed no less than 4 weeks following the initial assessment of response. Tumor assessment at the Off-Treatment Visit is only necessary for subjects who discontinue study drug without disease progression if more than 4 weeks have passed since the previous assessment (window for these assessments is within 1 week of the Off-Treatment Visit).

   Follow-up Period: If a subject discontinues from study treatment without disease progression, tumor assessments should continue to be performed every 8 weeks until documentation of disease progression, beginning a new anticancer treatment or data cut off for the primary analysist. During the Follow-Up Period, scans will no longer be sent to the ICL.

o. A bone scan (^{99}m-technetium-based scintigraphy, whole body bone MRI, or ^{18}F-NaF PET) to assess bone metastases will be performed within 6 weeks prior to randomization (historical scans prior to signing informed consent are acceptable) to establish a baseline, and then every 24 weeks (within the 24th week) from randomization, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR, a bone scan will be required within a target of 1 week but no more than 2 weeks after achievement of CR to exclude new bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability.
Lesions identified on bone scans should be followed at all tumor assessment time points with cross-sectional imaging).
p. Screening CT of the brain with contrast or MRI of the brain pre- and post-gadolinium should be performed within 28 days of randomization. Subjects with protocol-eligible treated brain metastases must also have brain CT/MRI performed at all tumor assessment time points (eg, every 8 weeks). For other subjects, brain scans should be performed as clinically indicated and to confirm CR. The same methodology (CT or MRI) and scan acquisition techniques that were used for the screening assessments should be followed during the Randomization phase. A brain scan will be performed within a target of 1 week but no more than 2 weeks following achievement of a CR.
q. HRQoL will be assessed at Baseline, on Day 1 of each subsequent cycle starting with Cycle 2, and at the Off-Treatment Visit. Every effort should be made to administer HRQoL surveys prior to study drug administration and before other assessments and procedures.
r. Telephone contact or clinic visit on Day 8 (±2 days) of Cycle 1 to assess subjects for development of early toxicity. An unscheduled visit may be requested by the investigator if deemed necessary.
s. Concomitant medications will be recorded from the Screening Visit through 28 days after the last dose of study drug. All anticancer therapy will be recorded until time of death or the data cutoff for the primary analysis unless not allowed to be provided due to confidentiality.
t. AEs and SAEs will be recorded from the signature of Informed Consent until 28 days after the last dose of study drug. SAEs, irrespective of relationship to study drug, must be reported as soon as possible but not later than 24 hours from the date when the investigator becomes aware of the event. Signs/symptoms related to disease progression should not be reported as AEs. During treatment interruption due to AEs, repeat AE assessments should be performed at least every 7 days (until restarting study drug administration).
u. PFS2 is defined as the time from randomization to the date of disease progression after next line of therapy or death from any cause, whichever occurs first. Subjects who discontinue treatment before the data cutoff for the primary analysis will be followed for survival every 12 weeks (±1 week) after the Off-Treatment Visit. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email.
v. A blood sample for biomarkers will be collected at Baseline (pre-treatment) and at predose at the following time points: C1D15, C2D1, C3D1, C4D1, C5D1 and C6D1. A sample should also be collected at the Off-Treatment Visit. The biomarker sample at the Off-Treatment Visit will not be collected after the data cutoff for the primary analysis.

Table 7 Schedule of Assessments After the Data Cutoff for the Primary Analysis

Phase	**After the Data Cutoff for the Primary Analysis All cycles are 8 weeks in duration**	
Period	**Study Treatment Period[a]**	**Off-Treatment Visit**
Procedures/Assessments		
Vital Signs[b]	X	As clinically indicated
Physical Examination[c]	X	As clinically indicated
12-Lead ECG[d]	As clinically indicated	As clinically indicated
Echocardiogram/MUGA scan[e]	As clinically indicated	As clinically indicated
Pregnancy Test for WOCBP[f]	X	X
Clinical Chemistry/hematology (local lab)[g]	X	As clinically indicated
Urine dipstick testing[h]	X	As clinically indicated
Study drug administration	Once daily	
Tumor assessments (CT/MRI)[i]	As per local standard of care	
Bone Scan[j]	As clinically indicated	
Brain scan (CT/MRI)[k]	As clinically indicated	
AE/SAE[l]	X	X
Concomitant medications[m]	X	X

a. Efforts should be made to conduct study visits on the day scheduled (±3 days). The study visit (and safety assessments) still needs to occur regardless of a study medication hold per the visit schedule.

b. Assessments will include vital signs (resting BP [including date and time of measurement], HR, RR and body temperature). After the data cutoff for the primary analysis, one BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. A diary will be provided to the subject to capture the blood pressure evaluations between study visits. See subsection for management of hypertensive subjects.

c. A symptom-directed physical examination during the study, as clinically indicated.

d. Single 12-lead ECG as clinically indicated. Subjects are suggested to be in the recumbent position for a period of 5 minutes prior to obtaining ECG.

e. An echocardiogram or MUGA scan to assess LVEF will be performed as clinically indicated

f. A serum or urine pregnancy test will be performed at Day 1 of every cycle, and at the Off-Treatment assessment in women of childbearing potential (ie, premenopausal and perimenopausal women who have been amenorrheic for less than 12 months).

g. Clinical laboratory assessments will be conducted at a local laboratory. Clinical chemistry and hematology results should be reviewed prior to

administration of study drug for all cycles. Assessments may be performed within 72 hours prior to the visit.

h. Urine dipstick testing for subjects should be performed preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site). For subjects with a dipstick proteinuria ≥2+, see section 9.4.2.3 for management of proteinuria.

i. After the data cutoff for the primary analysis: Tumor assessments using contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis and other areas of known disease at screening or newly suspected disease should be performed as per local standard of care but not less frequently than every 12 weeks or earlier if clinically indicated. The same methodology (CT or MRI) and scan acquisition techniques that were used for the assessment during the Prerandomization and Randomization Phases should be used after the data cutoff for the primary analysis. Scans will no longer be sent to the imaging core lab after the data cutoff for the primary analysis.

j. A bone scan to assess bone metastases should be performed as clinically indicated.

k. Subjects with protocol-eligible treated brain metastases should also have brain CT/MRI performed as per local standard of care. For other subjects, brain scans should be performed as clinically indicated.

l. All AEs leading to study drug discontinuation and SAEs will be recorded until 28 days after the last dose of study drug. SAEs, irrespective of relationship to study drug, must be reported as soon as possible but not later than 24 hours from the date when the investigator becomes aware of the event.

m. Concomitant medications will be recorded until 28 days after last dose.

9.5.2.1 Description of Procedures/Assessments Schedule

Refer to Table 6 for a description and timing of each procedure and assessment in the Prerandomization and Randomization Phase and to Table 7 for procedures and assessments after the data cutoff for the primary analysis.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of metastatic RCC. The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urine dipstick testing, 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 24 hours 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 28 days after the subject's last dose. 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 24 hours 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.

For sites in the US, 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 and/or the designated CRO, depending on responsibility for regulatory documents, 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 the estimated date of conception is either before the last visit or within 8 weeks of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 8 weeks 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 24 hours from when 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 24 hours from when the investigator becomes aware of the event 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 the

healthcare professional, subject, or consumer. Such events may be related to professional practice, healthcare products, occupational exposure, procedures, or systems, including prescribing, order communication, product labeling/packaging/nomenclature, compounding, dispensing, distribution, administration, education, monitoring, or use.

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.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) 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

As of 14 Jul 2018, the subjects' treatment assignment is no longer blinded.

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.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

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 6) and Schedule of Assessments After the Data Cutoff for the Primary Analysis (Table 7).

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 primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason may not be replaced.

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 (based on the data cut off for the primary analysis) and the database is locked and released. The interim analyses will be performed by an independent statistical reporting team. 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 ENDPOINTS

- Objective response rate at Week 24 (ORR_{24W}) as assessed by the investigator according to RECIST 1.1 (Appendix 8). ORR_{24W} is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) at the Week-24 (after randomization) time point or earlier. To be considered a BOR, all responses must be confirmed no less than 4 weeks after the initial assessment of response.
- Proportion of subjects with intolerable Grade 2 or any ≥ Grade 3 TEAEs within 24 weeks after randomization (as of the Week-24 time point).

9.7.1.1.2 SECONDARY ENDPOINTS

- Progression-free survival (PFS), defined as the time from the date of randomization to the date of first documentation of disease progression or date of death or the date of data cutoff for the primary analysis, whichever occurs first. PFS censoring rules will be defined in the statistical analysis plan (SAP) and will follow FDA guidance.
- ORR as assessed by the investigator according to RECIST 1.1 at the end of treatment. ORR is defined as the proportion of subjects with BOR of CR or PR at the end of treatment. To be considered BOR, all responses must be confirmed no less than 4 weeks after the initial assessment of response.
- Overall safety profile and tolerability of lenvatinib in combination with everolimus.
- Proportion of subjects who discontinue treatment due to toxicity, defined as the proportion of subjects who discontinue study treatment due to TEAEs.

- Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a subject discontinues study treatment due to TEAEs.
- Lenvatinib and everolimus exposure parameters and PK and PD drug-drug interactions.
- Overall survival (OS), measured from the date of randomization until date of death from any cause. In the absence of confirmation of death, subjects will be censored either at the date that the subject was last known to be alive or the date of data cutoff for the primary analysis, whichever comes earlier.
- Health-Related Quality of Life (HRQoL) will be assessed using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L instruments.
- PFS2, defined as the time from randomization to the date of disease progression after next line of therapy or death from any cause or the date of data cutoff for the primary analysis, whichever occurs first. PFS2 censoring rules will be defined in the SAP.

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Tumor response endpoints ORR_{24W}, ORR, and PFS based on IIR assessment. These endpoints will be defined in the same way as those based on the investigator assessments.
- Associations between blood biomarker and efficacy related endpoints.
- Development of exposure/biomarker/clinical endpoint models (whenever possible, using a mechanism-based approach) for both efficacy and safety data.

9.7.1.2 Definitions of Analysis Sets

Full Analysis Set will include all randomized subjects. This will be a secondary analysis set for efficacy endpoints, which will be analyzed according to the treatment randomized, regardless of the treatment actually received.

Per-Protocol Analysis Set 1 will include all randomized subjects minus the 32 subjects who had received ≥2 incorrect lenvatinib doses due to IxRS issues. This will be the primary analysis set for efficacy endpoints, which will be analyzed according to the treatment randomized.

Per-Protocol Analysis Set 2 will include all subjects who received at least 1 dose of study drug, had no major protocol deviations, and had both baseline and at least 1 post-baseline tumor assessment. Subjects for whom death occurred before the first post-baseline tumor assessment will also be included. The Per-Protocol Analysis Set 2 will be a secondary analysis set for efficacy endpoints. The 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues are considered as having experienced major protocol deviations and will be excluded from the Per-Protocol Analysis Set 2. (A 33rd subject received a single incorrect lenvatinib dose due to IxRS issues, but given the brief exposure of the incorrect [slightly higher] dose before detection and correction, and because there were no adverse

effects, this subject will be considered to have experienced a minor protocol deviation and will not be excluded from analysis sets.)

Safety Analysis Set will include all subjects who were randomized and received at least 1 dose of study drug. This will be the analysis set for all safety evaluations, which will be analyzed according to the treatment actually received.

Per-Protocol Safety Analysis Set will include all treated subjects in Per-Protocol Analysis Set 1. This will be the primary analysis set for the primary safety endpoint, which will be analyzed according to the treatment actually received.

Pharmacokinetic (PK) Analysis Set will include all subjects who received at least 1 dose of study drug with documented dosing history and have at least 1 evaluable lenvatinib plasma or everolimus whole blood concentration data.

Pharmacodynamic Analysis Set will include all subjects who received at least 1 dose of study drug with documented dosing history and have at least 1 evaluable pharmacodynamic data.

For the Pharmacokinetic, Pharmacodynamic and other Biomarker endpoints, their respective analysis plans will specify if the analysis set will or will not include the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues

Quality of Life (QoL) Analysis Set will consist of all subjects who have any QoL data.

The analysis sets are summarized in the following table.

Analyses for:	**Efficacy Parameters**	**Safety Parameters**
Analysis Set:	**Full Analysis Set**	**Safety Analysis Set**
Definition:	All subjects randomized	All randomized subjects who received at least 1 dose of study drug
Used as:	A secondary analysis set for efficacy endpoints	An analysis set for safety parameters
Analysis Set:	**Per-Protocol Analysis Set 1**	**Per-Protocol Safety Analysis Set**
Definition:	All randomized subjects minus the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues	All treated subjects minus the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues
Used as:	The primary analysis set for the primary efficacy endpoint	The primary analysis set for the primary safety endpoint
	An analysis set for the secondary efficacy endpoints	An analysis set for other safety parameters
For interim analyses:	The analysis set for the planned 2 interim analyses of the primary efficacy endpoint	The analysis set for the planned two interim analyses of the primary safety endpoint

Analysis Set	Per-Protocol Analysis Set 2	
Definition	All randomized subjects who received at least one dose, had no major protocol deviation, and had both baseline and at least 1 post-baseline tumor assessment. Subjects for whom death occurred prior to the first post-baseline tumor assessment will also be included.	
Used as	An analysis set for a sensitivity analysis of the primary efficacy endpoint	An analysis set for a sensitivity analysis of the primary safety endpoint
	An analysis set for the secondary efficacy endpoints	

9.7.1.3 Subject Disposition

Subject disposition will be summarized for the Per-Protocol Analysis Set 1, Per-Protocol Analysis Set 2, and Full Analysis Set. All subjects who were screened for the study will be accounted for and reported in the study results. The reasons for screen failures will be described and documented by subject and summarized by total number of subjects with screen failures. If deemed relevant, the reasons for excluding subjects will be evaluated to determine if these reasons could help clarify the appropriate subject population for eventual drug use.

The number (percentage) of randomized and treated subjects will be summarized as well as subjects who completed the study/discontinued from the study and reasons for discontinuation by treatment arm. The number (percentage) of subjects who completed the study treatment/discontinued from the study treatment and reasons for discontinuation will also be summarized by treatment arm.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the Per-Protocol Analysis Set 1, Per-Protocol Analysis Set 2, and Full Analysis Set. For continuous demographic/baseline variables including age, weight, and height, results will be summarized and presented as N, mean, standard deviation, median, Q1, Q3, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

9.7.1.5 Prior and Concomitant Therapy

Prior and concomitant therapy will be summarized for the Per-Protocol Analysis Set 1 and Full Analysis Set. All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications will be defined as medications that were started prior to the first dose of study drug and were stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that (i) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (ii) started on or after the date of the first dose of study drug up to 28 days following the last dose in randomization phase. Medications that cannot be determined

to be prior/concomitant/posttreatment due to missing or incomplete dates will be regarded as concomitant.

Prior medications will be summarized by anatomical class (Anatomical Therapeutic Chemical [ATC] Level 1), pharmacologic class (ATC Level 3), and World Health Organization (WHO, Geneva, Switzerland) generic drug name by frequency counts and percentages. The same summary will be provided for concomitant medications except thyroxine suppression therapy and hypertensive therapy. Concomitant thyroxine suppression therapy and hypertensive therapy will be summarized separately. In addition, there also will be a separate summary for the concomitant medications of P-glycoprotein inhibitors and/or inducers. Data listings will be provided for all prior and concomitant medications, for all concomitant thyroid suppression therapy, for all concomitant hypertensive therapy, and for all concomitant P-glycoprotein inhibitors and/or inducers.

9.7.1.6 Efficacy Analyses

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Primary analysis of ORR_{24W} will be based on a non-inferiority test. There will be two interim analyses and the primary analysis. The two interim analyses will be performed using only Per-Protocol Analysis Set 1. The primary analysis will be performed using the Per-Protocol Analysis Set 1 as the primary analysis set and will also be performed using Per-Protocol Analysis Set 2 and the Full Analysis Set as secondary analysis sets. At each interim analysis and primary analysis, the point estimate of ORR_{24W} for each treatment group (18 mg and 14 mg) will be summarized with the corresponding 95% confidence interval (CI). The odds ratio of ORR_{24W} (14 mg vs 18 mg) along with the 90% CI will be calculated using the Cochran-Mantel-Haenszel (CMH) method stratified by MSKCC prognostic groups and prior PD-1/PD-L1 treatment. Non- inferiority in ORR_{24W} will be claimed if the O'Brien-Fleming efficacy boundary is crossed at either interim analysis or primary analysis based on the results from the Per-Protocol Analysis Set 1. If the 1-sided *P*-value is ≤ 0.005 at the first interim analysis, or ≤ 0.014 at the second interim analysis, or ≤ 0.045 at the primary analysis, non-inferiority in ORR_{24W} will be claimed. Futility will be claimed if the futility boundary is crossed. If the 1-sided *P*-value is ≥ 0.776 at the first interim analysis, or ≥ 0.207 at the second interim analysis, futility will be claimed. The treatment difference in ORR_{24W} for 14 mg vs 18 mg will also be estimated along with 90% CIs based on the asymptotic normal approximation.

At each interim analysis and at the primary analysis, if the noninferiority boundary of the primary efficacy endpoint is crossed, the analysis of the primary safety analysis will be performed for Per-Protocol Safety Analysis Set. The primary safety endpoint is the proportion of subjects with intolerable Grade 2 or any $\geq$ Grade 3 TEAEs within 24 weeks after randomization (as of the Week-24 time point). Frequency (number and percentage) will be summarized for intolerable Grade 2 or any $\geq$ Grade 3 TEAEs within 24 weeks after randomization by treatment. The proportions will be tested using the CMH test (2-sided alpha=0.05), stratified by MSKCC prognostic groups and prior PD-1/PD-L1 treatment. The proportions of the primary safety endpoint will also be summarized for Safety Analysis Set for descriptive purpose.

To explore homogeneity of treatment effect across centers/regions, sensitivity analyses will be conducted to adjust center/region effect for the primary endpoints of ORR_{24W} and proportion of subjects with intolerable Grade 2 and any ≥Grade 3 TEAEs within 24 weeks after randomization using logistic regression models, including center/region as a covariate.

Determination of whether 14 mg lenvatinib can be used as an alternative dosing strategy will be based on clinical judgment by the sponsor in consultation with the independent DMC (as specified in the DMC charter) by assessing risks and benefits according to the totality of the safety and efficacy data.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

All secondary efficacy endpoints will be summarized descriptively for the Per-Protocol Analysis Set 1, Per-Protocol Analysis Set 2, and Full Analysis Set. The median PFS and PFS2 will be calculated using the KM product-limit estimates for each treatment group and presented with 2-sided 95% CIs. The KM estimate of PFS will also be plotted over time for each treatment group.

Point estimate of ORR and 95% CI will be summarized for each treatment arm. Odds ratio with 90% CI will be estimated using the CMH method stratified by MSKCC prognostic groups and prior PD-1/PD-L1 treatment.

The median survival time and the survival rates at 12, 18, and 24 months will be calculated using KM product-limit estimates for each treatment group and presented with 2-sided 95% CIs. The KM estimates of OS will be plotted over time.

For HRQoL analyses, summary statistics of the scores for the derived functional/symptom scales according to the scoring manual and global health status scores will be summarized by treatment arm at each time point. A separate pre-specified HRQoL analysis following FDA and EMEA patient-reported outcome (PRO) guidelines will be performed and detailed in a separate SAP and HRQoL report. Scoring of EQ-5D-3L and derivation of utility for health economic analysis will also be accomplished in a separate analysis and described in a separate HRQoL report.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

All exploratory endpoints will be summarized descriptively. Exploratory efficacy response endpoints ORR_{24W}, ORR, and PFS based on IIR assessment will be summarized using the same statistical methods as those used for the same response parameters based on the investigator assessments.

9.7.1.6.4 HANDLING OF MISSING DATA FOR EFFICACY ANALYSES

For efficacy endpoints related to ORR which summarizes the percentage of responders, missing responses will not be imputed and subjects with missing response will be considered as non-responders. For incomplete dates involving efficacy data, a conservative imputation rule will be used for calculation if needed. Details of handling missing data and imputation rules will be specified in SAP and further in the study analysis dataset specifications.

HRQoL analysis will follow FDA and EMEA PRO guidelines. Handling of missing values for HRQoL analyses will be detailed in a separate SAP and HRQoL report.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, and Other Biomarker Analyses

Lenvatinib and everolimus concentrations will be summarized by use of descriptive statistics and plotted as appropriate for each treatment group.

Concentrations of lenvatinib in plasma and everolimus in whole blood will be pooled with existing data from other completed studies and analyzed using a population PK approach to estimate population PK parameters for each drug. The analyses will be detailed in a separate analysis plan.

9.7.1.7.1 PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Lenvatinib and everolimus exposure parameters (AUC or concentration at the time of the event or cumulative AUC, as appropriate) derived from the population PK analysis will be related to biomarker, safety, and efficacy data using a model-based approach. For some PK/PD analyses, data from this study will be pooled with data from the Phase 2 Study E7080-G000-205 (Study 205).

For the exposure-response relationship for biomarkers (e.g., VEGF, Ang-2), data will be analyzed using a model-based approach with indirect PK/PD models.

For efficacy, a tumor growth inhibition model based on longitudinal tumor size measurements of target lesions will be included. Study drug exposure for lenvatinib and everolimus and/or measured biomarkers (e.g., VEGF, Ang-2) will be investigated as predictors and/or correlations with tumor burden changes in the tumor growth inhibition model, whenever possible using a mechanism-based approach.

Other analyses will include logistic regression analysis for ORR_{24W}, KM plots of PFS data, and Cox-regression analysis. For the Cox-regression analysis of PFS, adjustment will be made for subject's baseline characteristics or tumor-related features. In addition to lenvatinib and everolimus exposure, changes in biomarker concentrations and/or tumor burden will be related to PFS, whenever possible using a mechanism-based approach.

For the exposure-response relationship of safety, the model-based analysis will include the following AEs: hypertension (systolic and diastolic BP), triglyceridemia (and cholesterolemia), glycemia, proteinuria, weight loss, fatigue, nausea, vomiting and diarrhea. For hypertension, triglyceridemia (and cholesterolemia) and glycemia, data will be analyzed using an indirect-response model. For proteinuria, urine dipstick and/or 24-hour urine data will be analyzed using a longitudinal categorical logistic regression analysis with Markov element. For weight loss, fatigue, nausea, vomiting, and diarrhea, data will be analyzed using a longitudinal categorical logistic regression analysis. For time to treatment discontinuation due to an AE and time to first dose reduction, KM plots stratified by lenvatinib exposure will be prepared.

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

9.7.1.7.2 BIOMARKER ANALYSES

The effect of lenvatinib and everolimus combination treatment on exploratory biomarkers will be summarized by treatment group. Associations between clinical outcomes and baseline biomarker levels, and/or change in levels from baseline will be explored. The analysis will be detailed in the biomarker analysis plan (BAP) and reported separately.

For exploratory endpoints, Pharmacokinetic, Pharmacodynamic and Other Biomarker endpoints, their respective analysis plans will specify if the analyses will and will not include the 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Per-Protocol Safety Analysis Set and Safety Analysis Set. All safety analyses will be summarized separately by treatment group. The incidence of TEAEs, intolerable Grade 2 TEAEs that lead to dose interruption, dose reduction, or drug discontinuation, ≥ Grade 3 TEAEs, and SAEs will be summarized; rates will be summarized using descriptive statistics.

Time to treatment discontinuation due to an AE, number of dose reductions, and time to first dose reduction will be summarized. The proportion of subjects who discontinue treatment due to toxicity will be summarized by frequency counts and percentages. Median, upper, and lower quintiles of time to treatment discontinuation due to toxicity will be summarized for subjects who discontinue study treatment due to TEAEs.

9.7.1.8.1 EXTENT OF EXPOSURE

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

9.7.1.8.2 ADVERSE EVENTS

Adverse events will be graded using CTCAE v4.03. 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 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 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.

An overview table, including the incidence of and the number of subjects with TEAEs, SAEs, deaths, and those TEAEs that led to study drug discontinuation, dose modification, or dose interruption will be provided.

The incidence of TEAEs will be summarized by system organ class (SOC), preferred term (PT), CTCAE grade, and relatedness to study drug. All summaries will be performed by treatment group. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only one time in the incidence count for that MedDRA term with the highest CTCAE grade (in the summary by CTCAE grade) or with the closest relationship to study treatment (in the summary by relatedness to study treatment).

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

In addition, the overall proportion of subjects with TEAEs of CTCAE Grade 3 or higher and the overall proportion of subjects with intolerable CTCAE Grade 2 TEAEs that result in dose modification will be summarized.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment arm using descriptive statistics. Laboratory parameters will be categorized according to CTCAE v4.03. Grades, and shifts from baseline CTCAE Grade to worst postbaseline Grade will be assessed using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and at least 1 postbaseline result.

Common Terminology Criteria for Adverse Events v4.03 (Appendix 3) will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). A more detailed definition of TEMAV will be specified in the SAP. A summary of TEMAVs will be presented by treatment arm.

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 and treatment group. Subjects will be included in the summary if they had both a Baseline value and at least 1 postbaseline value.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and by treatment group. Shift tables will present changes from baseline in ECG

interpretation (categorized as normal; abnormal, not clinically significant; and abnormal clinically significant).

9.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive summary statistics for LVEF assessed on echocardiogram or MUGA scans and changes from baseline will be calculated and summarized by treatment group.

9.7.2 Determination of Sample Size

The objective of the study is to assess whether a starting dose of lenvatinib 14 mg QD in combination with everolimus 5 mg will provide comparable efficacy with an improved safety profile compared to lenvatinib 18 mg in combination with everolimus 5 mg. Determination of whether 14 mg lenvatinib can be used as an alternative dosing strategy will be based on clinical judgment by the Sponsor in consultation with the independent DMC (as specified in the DMC charter) by assessing risks and benefits according to the totality of data at either of the interim or primary analyses. Nevertheless, the sample size is guided by the plan of testing non-inferiority on the primary efficacy endpoint and superiority on the primary safety endpoint. The details and assumptions are provided below.

Sample size is based on detecting both the non-inferiority of ORR_{24W} and superiority of the primary safety endpoint of the proportion of subjects with intolerable Grade 2 or any ≥ Grade 3 TEAEs within 24 weeks after randomization in comparison of the 14-mg arm to the 18-mg arm (Appendix 13).

Non-Inferiority of ORR_{24W} Comparing the 14-mg Arm to the 18-mg Arm

Based on the assumption from Study 205 that the confirmed ORR for the 18 mg lenvatinib + 5 mg everolimus arm is 37% (19 responders out of N=51) vs 6% for the everolimus arm (3 responders out of N=50), the 95% CI of the odds ratio comparing everolimus vs. lenvatinib 18 mg + everolimus arm is (0.029, 0.395). The non-inferiority margin is chosen to ensure that a reasonable fraction of the lenvatinib 18 mg + everolimus vs. everolimus treatment effect is preserved. A 70% retention of the treatment effect of lenvatinib 18 mg + everolimus vs. everolimus is used for this design. Following the approach in Rothmann, et al. (2003), using the 95% CI upper limit method based on logarithm of the odds ratio, the non-inferiority margin is estimated as

$\exp((1-\delta) * (upper\ limit\ of\ 95\%\ CI\ of \log odds\ ratio\ (eve\ /lenv\ 18\ mg +\ eve\ )))$, where $0 < \delta < 1$ is the retention rate.

To retain 70% of the lenvatinib 18 mg + everolimus vs. everolimus treatment effect, the non-inferiority margin of the odds ratio is estimated to be

$\exp\big((1-0.7) * log(0.395)\big) = 0.76$ (ie, Ha: OR (14 mg/18 mg)> M). Listed below are the non-inferiority margins on the scale of difference in ORR_{24W} between the lenvatinib 14-mg + everolimus arm and the lenvatinib 18-mg + everolimus arm corresponding to a 0.76 non-inferiority margin on the odds ratio scale for a different ORR_{24W} in the lenvatinib 18-mg + everolimus arm.

ORR_{24W} in the Lenvatinib 18-mg Arm	Non-inferiority Margin on Difference Scale (Lenvatinib 14-mg ARM – Lenvatinib 18-mg ARM)
10%	-0.02
20%	-0.04
30%	-0.05
40%	-0.06
50%	-0.07
60%	-0.07

Two interim analyses will take place when 150 and 200 total subjects in the Per-Protocol Analysis Set 1 have completed 24 weeks follow-up or discontinue earlier. Each interim analysis will test both non-inferiority and futility of the 14-mg arm ORR_{24W} compared to the 18-mg arm ORR_{24W}. An O'Brien-Fleming stopping boundary will be used for non-inferiority. An interpolated non-binding stopping boundary will be used for futility, which will spend $\beta=0.005$ and $\beta=0.10$ at the first and second interim analysis, respectively. Assuming 37% ORR_{24W} in the lenvatinib 18-mg arm and 45% ORR_{24W} in the lenvatinib 14-mg arm, and adjusting for the interim analyses, a total of 306 subjects (153 per arm) in the Per-Protocol Analysis Set 1 is required to achieve 80% statistical power at 1-sided $\alpha = 0.05$ (East 6 User Manual, 2014).

The stopping boundaries on the *P*-value scale and the cumulative error probabilities spent at each interim analysis and primary analysis are shown in the table below. For example, at the second interim analysis, non-inferiority in ORR_{24W} will be claimed if the 1-sided *P*-value is ≤ 0.014; futility will be claimed if the 1-sided *P*-value is ≥ 0.207.

Analysis No.	Cumulative α Spent	Efficacy Boundary (*P*-value)	Cumulative β Spent	Futility Boundary (*P*-value)
Interim Analysis #1	0.005	0.005	0.005	0.776
Interim Analysis #2	0.015	0.014	0.10	0.207
Primary Analysis	0.05	0.045	0.2	0.045

Superiority of Primary Safety Endpoint Comparing 14-mg Arm to 18-mg Arm:

At each interim analysis and the primary analysis in the Per-Protocol Safety Analysis Set, safety will be evaluated if the non-inferiority boundary is crossed. Assuming 75% subjects with intolerable Grade 2 or above TEAEs within 24 weeks after randomization in the 18-mg arm, with a total of 306 subjects, a superiority test at 2-sided $\alpha=0.05$ will give 80% statistical power to detect a 15% drop in proportion of subjects with intolerable Grade 2 or above TEAEs within 24 weeks after randomization in the 14 mg-arm.

In consideration of both the primary efficacy and safety endpoints, a total of approximately 306 subjects were originally planned to be randomized in a 1:1 ratio to both treatment arms. Since there were 32 subjects who received ≥2 incorrect lenvatinib doses due to IxRS issues, the number of subjects to be randomized will be increased by 32 to a total of approximately 338. Therefore, there will be approximately 306 subjects in the Per-Protocol Analysis Set 1.

Randomization will be stratified by MSKCC prognostic groups (favorable, intermediate, and poor risk) and whether subjects have had a prior PD-1/PD-L1 treatment (yes or no).

9.7.3 Interim Analyses

Safety and efficacy monitoring will be performed by an independent DMC. The function and membership of the DMC will be described in the DMC charter. Minutes from the open meetings of the DMC will be provided to regulatory agencies, if requested.

Two interim analyses will take place when 150 and 200 total subjects in the Per-Protocol Analysis Set 1 have completed 24 weeks follow-up or discontinue earlier. Each interim analysis will test both non-inferiority and futility of the 14 mg-arm ORR_{24W} compared to the 18 mg-arm ORR_{24W}. An O'Brien-Fleming stopping boundary (Lan and DeMets, 1983; DeMets and Ware, 1980) will be used for efficacy. An interpolated non-binding stopping boundary will be used for futility, which will spend β=0.005 and β=0.10 at the first and second interim analyses, respectively. The interim analyses will be performed by an independent statistical reporting team.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

AFINITOR® (everolimus) Package Insert:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022334s034lbl.pdf

LENVIMA® (lenvatinib) Package Insert:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206947s003lbl.pdf

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Rothmann M, Li N, Chen G, Chi GYH, Temple RT, Tsou HH. Design and analysis of non-inferiority mortality trials in oncology. Stat Med. 2003;22(2):239-64.

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CTCAE Reference

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-1 4_QuickReference_8.5x11.pdf.

RECIST Reference

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

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/IEC (or if regionally required, the head of the medical institution) 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 (or, if regionally required, the head of the medical institution) 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 (or if regionally required, the head of the medical institution) 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, 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 (eg, urine pregnancy test result documentation and urine dip-sticks)
- 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 correction 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 drug 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 drug, outcome).

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) 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). In addition, since the study was unblinded in July 2018, the sponsor will send a list of treatment codes by study subject to the investigator. 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 designated contractor 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 futility 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 Creatinine Clearance Estimate by Cockcroft-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 and Gault MH. 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 2 Clinical Studies Evaluating Drug-Drug Interactions with Lenvatinib

Nonclinical studies identify CYP3A4 as a potentially important Cytochrome P450 isozyme responsible for metabolism of lenvatinib. Clinical studies were conducted to test these findings.

Simultaneous CYP3A4/P-glycoprotein (P-gp) inhibition by ketoconazole slightly (15% to 19%) increases systemic exposure to lenvatinib (Shumaker, et al., 2015). Since no change was observed in half-life, t_{max}, or lag time (t_{lag}), the slight increase in systemic exposure is probably related to a decrease in first pass metabolism. However, since the magnitude of change is small, co-administration of lenvatinib with CYP3A4/P-gp inhibitors is not of clinical concern.

The influence of P-gp inhibition on lenvatinib PK has been investigated. P-gp inhibition was accomplished by co-administering a single dose of rifampin with a single dose of lenvatinib. Preliminary results suggest P-gp inhibition increases systemic exposure to lenvatinib 26% to 32%. Thus, co-administration of lenvatinib with P-gp inhibitors only causes a small increase in lenvatinib exposure.

The influence of simultaneous P-gp and CYP3A4 induction on lenvatinib PK has been investigated. Examination of simultaneous P-gp and CYP3A4 induction on lenvatinib PK was accomplished by administering rifampin QD for 21 days (Shumaker, et al., 2014). A single dose of lenvatinib was co-administered with the 15th dose of rifampin. Based on preliminary data, simultaneous P-gp and CYP3A4 induction minimally altered lenvatinib exposure as mean C_{max} increased about 8% while AUC decreased about 7%. Co-administration of lenvatinib with CYP3A4/P-gp inducers is not of clinical concern.

The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (LENVIMA® Package Insert).

Appendix 3 Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

The Common Terminology Criteria for Adverse Events (CTCAE v4.03, published 14 June 2010) provides descriptive terminology to be used for adverse event 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 adverse event terms in CTCAE v4.03 have been correlated with single-concept Medical Dictionary for Regulatory Activities (MedDRA) terms.

The Common Terminology Criteria for Adverse Events v4.03 grading refers to the severity of the AE. The Common Terminology Criteria for Adverse Events grades 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

ADL = activities of daily living, 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: Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)]. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-1 4_QuickReference_8.5x11.pdf.

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddra.org

Appendix 4 Karnofsky Performance Status

Karnofsky Performance Status Scale		
Definitions	**Rating (%)**	**Criteria**
Able to carry on normal activity and to work: No special care needed	100	Normal no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with efforts; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70	Cares for self; unable to carry on normal activity or to do active work
	60	Requires occasional assistance, but is able to care for most of his/her personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self. Requires equivalent of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospital admission is indicated although death not imminent
	20	Very sick; hospital admission necessary; active supportive treatment necessary
	10	Moribund; fatal process progressing rapidly
	0	Death

Source: Mor V, Laliberte L, Morris JN, et al. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. Cancer 1984;53:2002-2007.

Appendix 5 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 heart failure patients based on cardiac functional capacity. Based on NYHA definitions, subjects are to be classified as follows:

Class	NYHA Status
Class I:	Patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
Class II:	Patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III:	Patients with cardiac disease resulting in marked limitation of activity; they are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV:	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NYHA = New York Heart Association.
Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Note: NYHA Classification only applies to subjects with underlying cardiac disease.

Appendix 6 MSKCC Risk Model Criteria

Determination of Prognostic Score in Previously-Treated Patients

Parameter	Risk Factor	Criteria Value	Subject Value	If subject value meets criteria value, enter 1
KPS	Low KPS	<80%		
Corrected Calcium*	High Corrected Calcium	≥10 mg/dL		
Hemoglobin	Low Hemoglobin	Males: ≤13 g/dL Females: ≤11.5 g/dL		
				Sum total of above = MSKCC Prognostic Score:

* Corrected Calcium = ([4 – serum albumin in g/dL] x 0.8 + serum calcium)

Risk Group Based on MSKCC Prognostic Score

Risk Group	MSKCC Prognostic Score
Favorable Risk	0
Intermediate Risk	1
Poor Risk	2 or 3

Source: Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004;22:454–63.

Appendix 7 Tumor, Node, and Metastasis Staging of Renal Cell Carcinoma

Primary tumors (T)

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 the 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 the 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 the Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional lymph nodes (N)

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

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic group

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T1-2	N1	M0
	T3	N0-1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

Source: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, et al. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer-Verlag; 2010.

Appendix 8 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Tumor response assessments in this clinical trial will use Response Evaluation Criteria in Solid Tumors (RECIST 1.1) based on the 2009 article by Eisenhauer, et al entitled, New Response Evaluation Criteria in Solid Tumors: revised RECIST guideline (version 1.1).

The sole modification to RECIST 1.1 to be implemented in this study is that chest x-rays may not be used to follow disease; only CT scans may be used to follow chest disease.

The Eisenhauer article, published in the European Journal of Cancer, is available online at: http://linkinghub.elsevier.com/retrieve/pii/S0959804908008733.

Appendix 9 Health-Related Quality of Life Questionnaire FKSI-DRS

FKSI -DRS

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
BRM 3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
RCC2	I have had blood in my urine	0	1	2	3	4

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Appendix 10 Health-Related Quality of Life Questionnaire EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): __ __ __ __ __ __
Today's date (Day, Month, Year): 31 __ __ __ __ __ __

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 11 Health-Related Quality of Life Questionnaire EQ-5D-3L

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

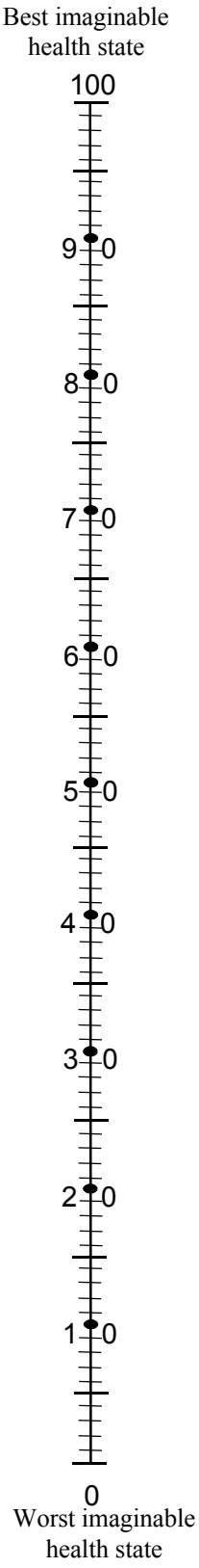
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 12 Pharmacodynamic and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

Sample collection for pharmacodynamic, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All pharmacodynamic and other biomarker samples will be single coded. Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID “key.”

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report, which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the pharmacodynamic and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, pharmacodynamic and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

Appendix 13 Efficacy and Futility Boundaries at Each Interim Analysis and the Primary Analysis

There will be 2 interim analyses and one primary analysis. The 2 interim analyses will be performed only in the Per-Protocol Analysis Set 1. The primary analysis will be performed in the Per-Protocol Analysis Set 1 as the primary analysis set, and will also be performed in the Per-Protocol Analysis Set 2 and in the Full Analysis Set as secondary analysis sets.

The tables below list the treatment differences in ORR_{24w} between the lenvatinib 14-mg + everolimus arm and the lenvatinib 18-mg + everolimus arm corresponding to the efficacy and futility boundaries at each interim analysis and primary analysis for different ORR_{24w} in the lenvatinib 18-mg + everolimus arm.

First interim analysis, non-inferiority stopping boundary OR = 1.788 (non-inferiority will be claimed if observed OR $\geq$1.788 at first interim analysis. Correspondingly, depending on $ORR_{24W,}$ non-inferiority will be claimed if observed treatment difference between the 14-mg arm and the 18-mg arm is $\geq \delta$).

ORR_{24W} in lenvatinib 18-mg arm	δ = Treatment difference (lenvatinib 14-mg arm - lenvatinib 18-mg arm)
10%	0.07
20%	0.11
30%	0.13
40%	0.14
50%	0.14
60%	0.13

First interim analysis, futility stopping boundary OR = 0.590 (futility will be claimed if observed OR $\leq$0.590 at first interim analysis. Correspondingly, depending on $ORR_{24W,}$ non-inferiority will be claimed if the observed treatment difference between 14-mg arm and 18-mg arm is $\leq \delta$)

ORR_{24W} in lenvatinib 18-mg arm	δ = Treatment difference (lenvatinib 14-mg arm - lenvatinib 18-mg arm)
10%	-0.04
20%	-0.07
30%	-0.10
40%	-0.12
50%	-0.13
60%	-0.13

Second interim analysis, non-inferiority stopping boundary OR = 1.436 (non-inferiority will be claimed if the observed OR ≥1.436 at second interim analysis. Correspondingly, depending on $ORR_{24W,}$ non-inferiority will be claimed if the observed treatment difference between the 14-mg arm and the18-mg arm is $\geq \delta$)

ORR_{24W} in lenvatinib 18-mg arm	δ = Treatment difference (lenvatinib 14-mg arm - lenvatinib 18-mg arm)
10%	0.04
20%	0.06
30%	0.08
40%	0.09
50%	0.09
60%	0.08

Second interim analysis, futility stopping boundary OR = 0.962 (futility will be claimed if the observed OR ≤0.962 at the second interim analysis. Correspondingly, depending on $ORR_{24W,}$ non-inferiority will be claimed if the observed treatment difference between the 14-mg arm and the18-mg arm is$\leq \delta$)

ORR_{24W} in lenvatinib 18-mg arm	δ = Treatment difference (lenvatinib 14-mg arm - lenvatinib 18-mg arm)
10%	-0.003
20%	-0.006
30%	-0.008
40%	-0.009
50%	-0.010
60%	-0.009

Primary analysis, OR = 1.128 (non-inferiority will be claimed if observed OR ≥1.128 at the primary analysis. Correspondingly, depending on $ORR_{24W,}$ non-inferiority will be claimed if the observed treatment difference between the 14-mg arm and the 18-mg arm is $\geq \delta$).

ORR_{24W} in lenvatinib 18-mg arm	δ = Treatment difference (lenvatinib 14-mg arm - lenvatinib 18-mg arm)
10%	0.01
20%	0.02
30%	0.03
40%	0.03
50%	0.03
60%	0.03

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7080-G000-218

Study Protocol Title: A Randomized, Open-Label (formerly Double-Blind), Phase 2 Trial to Assess Safety and Efficacy of Lenvatinib at Two Different Starting Doses (18 mg vs 14 mg QD) in Combination With Everolimus (5 mg QD) in Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment

Investigational Product Name: Lenvatinib (E7080), everolimus

IND Number: 124564

EudraCT Number: 2016-002778-11

SIGNATURES

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16 Sept. 2020
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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-G000-218
Study Protocol Title:	A Randomized, Open-Label (formerly Double-Blind), Phase 2 Trial to Assess Safety and Efficacy of Lenvatinib at Two Different Starting Doses (18 mg vs 14 mg QD) in Combination With Everolimus (5 mg QD) in Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment
Investigational Product Name:	Lenvatinib (E7080), everolimus
IND Number:	124564
EudraCT Number:	2016-002778-11

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 on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date