1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-G000-307
Study Protocol Title:	A Multicenter, Open-label, Randomized, Phase 3 Trial to **C**ompare the Efficacy and Safety of **L**envatinib in Combination with **E**verolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with **A**dvanced **R**enal Cell Carcinoma (**CLEAR**).
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, pembrolizumab, and sunitinib
Indication:	Renal Cell Carcinoma
Phase:	3
Approval Dates:	Original Protocol: 22 Jun 2016 Protocol Amendment 01: 26 Sep 2016 Protocol Amendment 02: 03 Feb 2017 Protocol Amendment 03: 10 Jan 2018 Protocol Amendment 04: 30 Jun 2018 Protocol Amendment 05: 19 Dec 2018 Protocol Amendment 06: 10 Sep 2019 Protocol Amendment 07: 06 Aug 2020
IND Number:	124564
EudraCT Number:	2016-000916-14
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.

REVSION HISTORY

Amendment 07

Date: 06 Aug 2020

Overall reason for the amendment: to remove the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) exploratory analysis for Arm B subjects.

Change	Rationale	Affected Protocol Sections
Removed the exploratory objective: ~~To assess PFS by IIR using immune related RECIST (irRECIST) in subjects treated with lenvatinib in combination with pembrolizumab.~~	Removed the irRECIST exploratory analysis due to low pseudoprogression rate with pembrolizumab in the renal cell cancer (RCC) population	Synopsis, Objectives Section 8.3
Removed the irRECIST assessment and criteria: ~~For subjects in Arm B only, tumor assessments will also be performed using irRECIST; this assessment will be performed by IIR following database lock for PFS analysis~~		Synopsis, Efficacy Assessments Section 9.5.1.2.1 Section 12, Appendix 7 (removed)
Removed the irRECIST exploratory endpoint and analysis: ~~Progression-free survival (PFS) as determined by IIR using irRECIST for subjects receiving lenvatinib plus pembrolizumab (Arm B), and defined as the time from the date of randomization to the date of the first documentation of confirmed immune-related progressive disease (irPD) or death (whichever occurs first).~~		Synopsis, Statistical Methods Section 9.7.1.1.3
~~Progression-free survival (PFS) using irRECIST as assessed by IIR for subjects receiving lenvatinib plus pembrolizumab (Arm B) will be summarized using K-M estimates.~~		Section 9.7.1.6.3

DATE	Highlights of Major Changes Sections/Changes
10 Sep 2019	**Amendment 06:**
	Title page, List of Abbreviations, and Section 5.2: Updated to current ICH name (International Council for Harmonisation of Technical Requirements for ~~Registration of~~ Pharmaceuticals for Human Use).
	Synopsis and Sections 9.1, 9.1.2, 9.1.2.1, 9.1.2.2, 9.1.3.1, 9.5.1.2.1: The end of the Randomization Phase, Treatment Period, and Follow-up period definitions are updated to reflect the changes in PFS analysis.
	Synopsis and Sections 9.5.1.2. 9.7.1.1.2, 9.7.1.6.1, 9.7.1.6.2, 9.7.2: Added an interim analysis of PFS projected to occur ~38 months after the first subject was randomized in study. The final PFS analysis is projected to occur approximately ~45 months after the first subject was randomized in the study. Based on the results from the two recent available IO+VEGF studies, an interim analysis of PFS is added. The number of interim analyses of OS is also increased from 1 to 3. The alpha-spending functions for PFS and OS analyses are added or updated. The procedure to control familywise error rate is changed to a graphical approach. The powers of statistical testing are re-calculated under the graphical approach. Updated median OS assumption for sunitinib arm from 30 months to 37.9 months and updated the projected timing for interim analyses and final analysis of OS accordingly. The projected timing for final analysis of OS is updated from 53 months to 69 months after first subject randomized.
	Synopsis and Section 9.7.3: Updated Table 9, Summary of Interim and Final Efficacy Analyses, to specify timing of interim and final analyses.
	Synopsis and Section 9.7.4: Multiplicity adjustment strategy changed from truncated Hochberg procedure to Graphical approach with initial alpha of 0.045 assigned to test PFS lenvatinib+pembrolizumab vs sunitinib and initial alpha of 0.0049 assigned to test PFS lenvatinib+everolimus vs sunitinib. The multiplicity test strategy was updated to optimize the probability of success of all hypothesis tests while to strongly control the familywise type I error rate under 0.05 (2-sided).

DATE	Highlights of Major Changes Section/Change
19 Dec 2018	**Amendment 05:**
	Synopsis and Section 9.5.1.2: During the EU member states Voluntary Harmonisation Procedure (VHP) regulatory authority review, the assessors' requested removal of the second course retreatment phase option for pembrolizumab. Since there are many second-line options available for advanced RCC, including checkpoint inhibitors, this has been agreed to be removed.
	Section 9.5.2: Removed Table 9, Schedule of Visits and Procedures in E7080-G000-307 – Second Course (Pembrolizumab Retreatment) Phase. Renumbered subsequent tables.
	Section 9.7.3: Updated Table 9, Summary of Interim and Final Efficacy Analyses, to clarify that the results of the planned interim analysis (IA1) of ORR and DOR may be considered for an early submission in regions outside of EMA jurisdiction.

DATE	Highlights of Major Changes Section/Change
30 Jun 2018	**Amendment 04:**
	Synopsis, Section 6, and Section 9.3: Increased the planned number of investigational sites to 200 to accommodate the delay in study enrollment.
	Synopsis, Sections 8.2 and 8.3: Updated secondary and exploratory objectives for consistency with the endpoints in Sections 9.7.1.1.2 and 9.7.1.1.3
	Synopsis, Section 9.1, Section 9.3, and Section 9.7.2: Increased the planned enrollment to 1050 subjects (approximately 350 subjects per arm) to address slow enrollment in the first 12 months and high loss of PFS event rate, and provide adequate power for intergroup comparisons of overall survival (OS).
	Synopsis, Section 9.1 and Section 9.7.2: Increased the estimated duration of the Study Randomization Period to 43 months (29-month enrollment period; 14-month follow-up period). Increased total study period to 53 months.
	Synopsis and Sections 9.1.2 and 9.1.3: Added reference to the Second Course (Pembrolizumab Retreatment) Phase and defined conditions for continuation of pembrolizumab with or without lenvatinib after discontinuation or completion of study treatment in Arm B.
	New Section 1.1.1: Added section to describe specific conditions under which subjects in Arm B may receive retreatment with pembrolizumab with or without lenvatinib, referred to as the Second Course Phase, after discontinuation or completion of pembrolizumab in this study.
	Synopsis and Section 9.3.2: Revised Exclusion Criterion no. 2 to clarify that central nervous system (CNS) metastases (not just brain metastases) must be stable for at least 4 weeks before starting study treatment. Added Exclusion Criterion no. 28 to exclude subjects who have had an allogenic tissue/solid organ transplant in accordance with current pembrolizumab label.
	Section 9.5.1.2: Added subheadings and included new Section 1.1.1.1.1 to provide requirements for tumor imaging during the Second Course (Pembrolizumab Retreatment) Phase
	Section 9.5.2: Added schedule of assessments and visits for the Second Course (Pembrolizumab Retreatment) Phase. Renumbered subsequent tables.
	Synopsis and Section 9.4.2.2: Added Management of Proteinuria subheading; added text to clarify that lenvatinib/sunitinib must be discontinued in the event of nephrotic syndrome, and to align with guidance in the current lenvatinib global investigator brochure.
	Synopsis and 9.7.1.6.1: For the primary analysis of PFS, α was decreased to 0.0499 for all comparisons, due to the addition of an interim analysis to which an α of 0.0001 was allocated. For the multiplicity adjustment, the *P*-value thresholds for the primary analysis of PFS were changed because of the addition of an interim analysis.

DATE	Highlights of Major Changes Section/Change
30 Jun 2018	**Amendment 04:**
	Synopsis and Section 9.7.2: Added justification for the sample size recalculation and power determination for ORR.
	Synopsis, 9.7.3: Two interim analyses were added: 1. A planned interim analysis of objective response rate (ORR) and duration of response (DOR) was added to include the first 88 treated subjects from the lenvatinib + pembrolizumab arm who complete a median follow-up of 12 months and have a minimum of 6 months follow-up for duration of response. 2. A planned interim analysis of OS was added to be performed at the time of the primary analysis for PFS.
	Section 9.4.8: Clarified the instructions for a missed dose of either lenvatinib or everolimus for subjects receiving lenvatinib + everolimus (Arm A). For subjects receiving lenvatinib + pembrolizumab (Arm B), the schedule for lenvatinib administration after pembrolizumab administration on Day 1 of Cycles 1 and 2 was revised for ease of study drug administration.
	Section 9.5.1.4.3: Clarified that urine microscopy should be performed at the institution's laboratory.
	Section 9.5.2, Table 7: A time window for the multigated acquisition (MUGA) scan and echocardiogram was added in footnote "l" for consistency with the Extension Phase. A time window for pharmacokinetic sampling was added in footnote "p."
	Section 9.7.1.6: Moved Figure 4 to Section 9.7.4.
	Section 9.7.2: Added information on the number of required death events and statistical analysis parameters for analysis of the key secondary endpoint of OS.
	Section 9.7.3: Specified that efficacy interim analyses will be conducted by the independent statistical group, that has no other responsibilities for the study.
	Added new Section 9.7.4: Added strategy to adjust for multiplicity and control of the overall family-wise error rate (FWER).
	Administrative changes to correct minor errors: Updated title page, List of Abbreviations, Section 5.2, and the Investigator signature page to add current ICH name (International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). Section 9.4.2.2, Section 9.5.1.2: minor text edits for consistency. Table 7 and Table 8: minor edits, including correction of cross-reference to footnote "c" in Table 8 for Day 15 assessment of vital signs and weight. Updated Reference List.

DATE	Highlights of Major Changes Section/Change
10 Jan 2018	**Amendment 03:**
	Sections 7.1.4, 7.2, and 9.4.7: Per EMA request, revised sections with updated data for Phases 1b/2 for the RCC cohort in Study 111, based on new cutoff date of 31 May 2017.
	Sections 8.2, 9.5.1.3, 9.7.1.1.2, 9.7.1.2, and 9.7.1.7.1, Table 7, and Synopsis: Text revised to clarify that no population pharmacokinetic (PK) analyses will be performed using pembrolizumab data in this study. Only comparisons to historical data will be performed. Pharmacodynamic (PD) data for pembrolizumab will not be measured. Per EMA request, added text that PK/PD analyses will be detailed in a separate analysis plan and references for the PK/PD analysis plan (CPMS-E7080-012P-v1) and the biomarker analysis plan (TSBM-E7080-307-ANA-1P) included in Section 9.5.1.3.2 of the protocol.
	Section 9.1.1.2: Revised time window for baseline assessments from Day 1 to within 72 hours prior to randomization
	Sections 9.1.2.1 and 9.1.3.1 and Synopsis: Revised text to clarify the conditions under which subjects will continue to receive study treatment
	Sections 9.1.2.2 and 9.1.3.2: Added text that defines the circumstances under which a subject is considered to be "lost to follow-up" and identifies the documentation needed to support this classification. Added text clarifying collection of survival status data.
	Section 9.3.1 and Synopsis: Revised inclusion criterion no. 7 for further clarity on adequate renal function. Added note to inclusion criterion no. 8, adequate bone marrow function, clarifying that conditions must be met without erythropoietin dependency or blood transfusion. Revised inclusion criterion no. 9 for further clarity.
	Section 9.3.2 and Synopsis: Revised exclusion criterion no. 6 (vaccination with live organism) for further clarity. Per EMA request, revised exclusion criterion no. 15 to change CV impairment window from 6 months to 12 months. Revised exclusion criterion no. 22, immunodeficiency, for further clarity.
	Section 9.3.3, Section 9.4.10.2 and Synopsis: Added text to clarify that subjects will continue to undergo tumor assessments and bone scans, and will be followed for survival unless lost to follow-up.
	Section 9.4.2.1, Section 9.5.1.4.4, Schedules of Assessments (Table 7 and Table 8) and Synopsis: Revised guidelines for management of hypertension as follows: • Requirement of repeat blood pressure (BP) measurements has changed. Repeat BP measurement now required only for subjects who have an elevated initial BP measurement as follows: systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg. • Definition of a BP assessment changed from 3 BP measurements to 2 BP measurements taken at least 5 minutes apart. • Time between BP assessments required for confirmation of hypertension changed from 2 BP assessments taken at least 1 hour apart to 2 BP assessments at least 30 minutes apart.

	• Clarified that subjects with uncontrolled hypertension (BP ≥160 mmHg or diastolic ≥100 mmHg) must have their BP monitored on Day 15 (or more frequently if clinically indicated) for 2 consecutive treatment cycles. Clarified that CTCAE grade is to be based solely on BP measurements.
	Section 9.4.2.2, Tables 6, 7 and 8, and Synopsis: Revised guidelines for management of proteinuria as follows: • Clarified that CTCAE grading for proteinuria will be based on a 24-hour urine result if available. • Added the option to use an immediate spot urine protein-to-creatinine ratio (UPCR) test as an alternative to a 24-hour urine protein test to quantify the 24-hour urine excretion if urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib/sunitinib dose level, or at the new dose level when there has been a lenvatinib/sunitinib dose reduction). • Specified that a 24-hour urine protein test is required if the UPCR result is ≥2.4 • Clarified that subjects with proteinuria ≥ 2+ should be tested on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.
	Section 9.4.2.11 and Synopsis: Revised guidelines for management of hemorrhage for further clarity.
	Section 9.4.3, Table 3, and Synopsis: Updated dose modification guidelines for pembrolizumab.
	Section 9.4.10.2 and Synopsis: Revised text pertaining to use of systemic glucocorticoids for further clarity.
	Section 9.5.1.2 and Synopsis: Clarified timing of screening scans.
	Section 9.7.1.2 and Synopsis: Added Pembrolizumab Pharmacokinetic Analysis Set
	Section 9.7.3: Per EMA request, clarified that DMC closed minutes will be provided after the end of the study.
	Administrative changes made throughout protocol: Updated List of Abbreviations, labeled Figure 1 in Section 7.1, corrected error in Figure 2, revised Tables 7 and 8 for consistency with text, corrected typographical errors, minor formatting changes.

DATE	**Highlights of Major Changes** **Section/Change**
03 Feb 2017	**Amendment 02:**
	Administrative changes made throughout the protocol: Minor reordering of text for consistency, minor text edits to sentences, paragraphs, table footnotes and sections throughout the protocol.
	Assessment of PFS based on investigator assessment per RECIST v.1.1 was added as a secondary objective and a secondary endpoint in the Synopsis, Section 8.2, and Section 9.7.1.1.2, as requested by the regulatory authorities. The following bullet was added as a Secondary Endpoint: "Progression-free survival (PFS) by investigator assessment is defined as the time from the date of randomization to the date of first documentation of disease progression based on

DATE	Highlights of Major Changes Section/Change
03 Feb 2017	**Amendment 02:**
	the investigator assessment per RECIST v.1.1 or death (whichever occurs first)." The following bullet was added under Secondary Objectives: "To assess PFS based on investigator assessment per RECIST v.1.1."
	A bullet under Secondary Objectives was revised to read "To compare safety and tolerability of treatment with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib, including the assessment of the proportion of subjects who discontinued treatment due to toxicity and time to treatment failure due to toxicity." (See Synopsis and Section 8.2.)
	Exclusion criterion 13 was adapted for the study indication (ie, carotid artery reference was deleted) in the Synopsis and Section 9.3.2. Exclusion criterion 27 was added to capture "known intolerance to any of the study drugs (or any of the excipients)," in the Synopsis and Section 9.3.2, as requested by the regulatory authorities.
	As requested by the regulatory authorities, "may be" was replaced with "if possible, will be" to confirm this intent in all appropriate and relevant sections. This change is reflected in the Synopsis, Section 9.5.1.3.2, and Section 9.7.1.7.3, as it applies to the various PK/pharmacodynamic evaluations, including PK/pharmacodynamic relationships (ie, exposure-efficacy, exposure-safety, and exposure-biomarker relationships) modeling.
	Dose-modification guidelines for holding treatment for pneumonitis were amended from Grade "3-4" to "3-4 or Recurrent 2." This change was made in the Synopsis and Table 3, Section 9.4.3.
	Synopsis and Section 9.7.1.2: The definition of The Pharmacodynamic Analysis Set was revised as follows: "…is the group of subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data to derive at least 1 pharmacodynamic measurement and with documented dosing history."
	Section 9.5.2, Table 7 and Table 8: As requested by the regulatory authorities, pregnancy assessment was added to the Follow-up Period. Footnote "n" in Table 7: "A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) at the Screening and Baseline Visits, on Day 1 of each cycle from Cycle 2 onwards, at the Off-Treatment Visit, and every 30 days up to 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first." In footnote "y," Table 7 and footnote "n" in Table 8, the statement "for subjects receiving treatment with pembrolizumab (Arm B)" was deleted. Footnote "i" in Table 8 was also revised to reflect this change. For consistency, Section 9.5.4.2 and the synopsis were amended to reflect this change.

DATE	Highlights of Major Changes Section/Change
03 Feb 2017	**Amendment 02:**
	Synopsis, Section 9.5.2 Table 7 (footnote "y") and Table 8 (footnote "n"), and Section 9.5.4.1: As requested by the regulatory authorities, the follow-up period for collecting SAE data was lengthened as follows: "SAEs regardless of causality assessment must be collected through the last visit and for 120 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier."
	Synopsis and Section 9.7.1.6.2: The following statement was added to the discussion of secondary efficacy analyses: "PFS by investigator assessment per RECIST v1.1 will be analyzed similarly as for the primary endpoint of PFS by IIR per RECIST v1.1." Text regarding PFS2 analysis was moved to the end of the secondary analyses section, following discussion of HRQoL to remain consistent with the order in which secondary objectives are presented.
	Synopsis and Section 9.7.1.7: The following statement, which applies to all PK/PD/biomarker analyses, was added: "The PK and PK/PD analyses will be detailed in a separate analysis plan that will be provided at a later date and the result will be provided in a standalone report."
	As requested by the regulatory authorities, Section 7.2 was revised from "Study Rationale" to "Study Rationale and Benefit Risk Assessment" and a benefit/risk statement was added.
	As requested by the regulatory authorities, the protocol language in the Synopsis and Section 9.1.2.2 was revised to specify that the sponsor may discontinue survival follow-up after completion of the primary study analysis when appropriate, eg, when only a minimal number of subjects remain in follow up.
	PK/PD objective was amended to read "To assess the PK/pharmacodynamic relationship between exposure and efficacy/biomarkers/safety, if possible, using a mechanistic approach." PK and PK/PD related exploratory objectives have been recategorized from exploratory to secondary, and the following secondary endpoints have been added to the Synopsis (Statistical Methods section) and Section 9.7.1.1.2 (Secondary Endpoints) as requested by the regulatory authorities: • Model-predicted clearance and AUC for lenvatinib in Arms A and B. • Model-predicted clearance and AUC for everolimus in Arm A, and pembrolizumab in Arm B. Text regarding PK and PK/PD analysis was moved to the end of the secondary analyses section in the Synopsis.

DATE	Highlights of Major Changes Section/Change
26 Sep 2016	**Amendment 01:**
	Administrative changes made throughout the protocol: Minor reordering of text for consistency, minor text edits to sentences, paragraphs, table footnotes and sections throughout the protocol. Replaced acronym for EMEA with EMA. Revised definition of end of study to the date of data cutoff for the final analysis or last subject/last visit, including discontinuation from study for any reason, whichever occurs later. This reflects the most recent definition in the protocol template.
	Recategorized PFS2 and HRQoL from exploratory objectives to secondary objectives in Synopsis and Sections 8.2 and 8.3, as requested by the EMA. Recategorized PFS2 and HRQoL from exploratory endpoints in Synopsis and Section 9.7.1.1.3 to secondary endpoints. Added proportion of subjects who discontinued treatment due to toxicity, and time to treatment failure due to toxicity as new secondary endpoints in Synopsis and Section 9.7.1.1.2 as requested by EMA.
	Exclusion criterion 19 changed and Exclusion Criterion 20 added in the Synopsis and Section 9.3.2 to clarify exclusion of subjects with a history of (noninfectious) pneumonitis requiring steroid treatment and exclusion of subjects with current pneumonitis. Exclusion Criterion 26 was added to exclude men who do not agree to use the methods of contraception specified in the protocol.
	Exploratory objective changed in the Synopsis and Sections 8.2 and 8.3 to indicate that duration of response will be summarized for subjects in all treatment groups and that no formal comparison will be performed.
	Text regarding the provision of DMC Meeting minutes has been added to the protocol in the Synopsis and Section 9.7.3 as requested by EMA.
	Clarified that serious adverse event reports, reports of pregnancy, reports of exposure to study drug through breastfeeding, and any follow-up information must be reported within 24 hours (Sections 9.5.4.1 and 9.5.4.2).
	More accurately described formulation, packaging, and supply of all investigational products in Synopsis and Section 9.4.5.
	Removed text on management of hypertension from Synopsis and Section 9.4.2.1, and text on management of GI perforation and fistula formation from Synopsis and Sections 9.4.2, 9.4.3, and 9.4.4. The text was removed for consistency with other lenvatinib protocols and to align with the study drugs' commercial labels. Hypertension and GI perforation/fistula formation should be managed at the discretion of the investigator.
	Reference added for method to be used to adjust for multiplicity and control family wise error rate, and text added to clarify the gatekeeping procedure in Sections 0 and 10.

DATE	Highlights of Major Changes Section/Change
26 Sep 2016	**Amendment 01:**
	Characterization of the population pharmacokinetics of pembrolizumab was added as an exploratory objective, and text additions and clarifications were made in the Synopsis, Sections 9.5.1.3.1, 9.7.1.2, and 9.7.1.7.1 and Table 7.
	Deleted FAST information that was inadvertently added to Appendix 3. Clarification of the New York Heart Association Cardiac Disease Classification was done in Appendix 4. Corrections to the Tumor, Node, and Metastasis Staging scheme were made in Appendix 5. Clarification in Appendix 7 that tumor assessment scans are performed every 8 weeks.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080

Name of Active Ingredient: Lenvatinib

Study Protocol Title

A Multicenter, Open-label, Randomized, Phase 3 Trial to **C**ompare the Efficacy and Safety of **L**envatinib in Combination with **E**verolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with **A**dvanced **R**enal Cell Carcinoma (**CLEAR**)

Investigators

Unknown

Sites

Approximately 200 sites worldwide

Study Period and Phase of Development

Approximately 69 months

Phase 3

Objectives

Primary Objective

The primary objective of the study is to demonstrate that lenvatinib in combination with everolimus (Arm A) or pembrolizumab (Arm B) is superior compared to sunitinib alone (Arm C) in improving progression-free survival (PFS) (by independent imaging review [IIR] using Response Evaluation Criteria in Solid Tumors [RECIST 1.1]) as first-line treatment in subjects with advanced renal cell carcinoma (RCC).

Secondary Objectives

- To compare objective response rate (ORR) by IIR using RECIST 1.1 of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.
- To compare overall survival (OS) of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.
- To compare safety and tolerability of treatment with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib, including the assessment of the proportion of subjects who discontinued treatment due to toxicity and time to treatment failure due to toxicity.
- To compare the impact of treatment on Health-Related Quality of Life (HRQoL) as assessed by using the Functional Assessment of Cancer Therapy Kidney Index-Disease-Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30, and the European Quality of Life (EuroQOL) EQ-5D-3L instruments, for subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib
- To assess PFS on next-line of therapy (PFS2) as reported by investigator.
- To assess PFS based on investigator assessment per RECIST v.1.1
- To characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with everolimus or pembrolizumab.
- To compare the PK of pembrolizumab from this study to historical data.

- To characterize the population PK of everolimus when co-administered with lenvatinib.
- To assess the PK/pharmacodynamic relationship between exposure and efficacy/biomarkers/safety, if possible using a mechanistic approach.

Exploratory Objectives

- To compare ORR by investigator assessment using RECIST 1.1.
- To assess the duration of response (DOR) by IIR and investigator assessment using RECIST 1.1 for subjects in all treatment arms.
- To compare the disease control rate (DCR) (complete response [CR] + partial response [PR] + stable disease [SD]) and clinical benefit rate (CBR) (CR, PR + durable SD) by IIR and investigator assessment using RECIST 1.1 of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.
- To compare PFS by IIR and investigator assessment using RECIST 1.1 in subjects treated with lenvatinib in combination with everolimus (Arm A) versus lenvatinib in combination with pembrolizumab (Arm B).
- To investigate the relationship between candidate tumor and blood biomarkers and clinical outcome measures including antitumor activity of study treatment.

Study Design

This is a multicenter, randomized, open-label, Phase 3 study to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line treatment in subjects with advanced RCC.

Approximately 1050 eligible subjects will be randomized to 1 of the following 3 treatment arms in a 1:1:1 ratio, with approximately 350 subjects in each arm:

- Arm A: lenvatinib 18 mg (orally, once daily) plus everolimus 5 mg (orally, once daily)
- Arm B: lenvatinib 20 mg (orally, once daily) plus pembrolizumab 200 mg (intravenously [IV], every 3 weeks [Q3W])
- Arm C: sunitinib 50 mg (orally, once daily) on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2)

Randomization will follow a predefined randomization scheme based on the following stratification factors: geographic region (Region 1: Western Europe and North America or Region 2: rest of the world) and Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate and poor risk).

Eisai will closely monitor patient dropout, including refusal of assignment. In the event that the dropout rate exceeds 5%, Eisai, in collaboration with the principal investigator(s), will consider capping the enrollment in the respective site(s) and/or region. The dropout plan will be detailed in a separate document.

The study will be conducted in 3 Phases: a Pre-randomization Phase, a Randomization Phase, and an Extension Phase.

The **Pre-randomization Phase** will consist of 2 periods: Screening and Baseline. The Pre-randomization Phase will last no longer than 28 days and will include the Screening Period to establish protocol eligibility and the 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 2 periods: Treatment Period and Follow-up Period. The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the planned final PFS analysis.

The **Treatment Period** for each subject will begin at the time of randomization and will end with the completion of the Off-Treatment Visit which will occur within 30 days after the final dose of study treatment.

Subjects will receive study treatment as continuous 21-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. Archival tumor tissue from the most recent surgery or biopsy will be collected (if available) from all enrolled subjects. Subjects will continue to receive study treatment until confirmed disease progression (PD) by independent review, development of unacceptable toxicity, subject request, withdrawal of consent, completion of 35 treatments with pembrolizumab (approximately 2 years), or study termination by the sponsor. Discontinuation of treatment may be considered for those subjects who fulfill all of the following criteria: attain a confirmed CR, have been treated for at least 8 cycles (at least 24 weeks) with pembrolizumab, and have received at least 2 treatments with pembrolizumab beyond the date when the initial CR is declared. In the presence of clinical benefit, subjects who complete treatment with pembrolizumab may continue to receive lenvatinib alone after this time point.

Subjects will be permitted to continue study treatment beyond RECIST 1.1-defined disease progression as long as the treating investigator considers that there is clinical benefit and the subject is tolerating study treatment. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the Eisai Medical Monitor. Subjects will discontinue study treatment upon evidence of further progression and/or loss of clinical benefit, as judged by the Investigator.

Disease progression must be confirmed by IIR by the imaging core laboratory (ICL) prior to the investigator discontinuing study treatment for a subject. In situations where the investigator judges that alternative treatments must be instituted immediately for a subject`s safety, study drug may be discontinued without waiting for independent review confirmation of radiographic evidence of disease progression. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

The **Follow-up Period** will begin the day after the Off-Treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent, is lost to follow-up, or the sponsor terminates the study. 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.

During the follow-up period, subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1 week) for PFS2, survival, and all subsequent anticancer treatments received. This information will be recorded unless this information is not allowed to be provided due to confidentiality. The sponsor may choose to discontinue survival follow-up following completion of the PFS analysis when appropriate, eg, when only a minimal number of subjects remain in follow up.

All subjects who discontinue study drug treatment prior to disease progression will continue to undergo tumor assessments every 8 weeks and a bone scan every 24 weeks in the Follow-up Period, until disease progression is documented and confirmed by independent review or a new anticancer therapy is initiated, unless the subject withdraws consent.

The end of the Randomization Phase of the study will be the data cutoff date for the planned final PFS analysis, which will occur when the target number of events (approximately 388 PFS events

as determined by the IIR) for each comparison has been observed. All subjects who are still on study treatment at that time will enter the Extension Phase.

The **Extension Phase** will consist of 2 periods: Treatment Period and Follow-up Period. In the **Treatment Period**, subjects still on study treatment following the data cutoff date of the planned final PFS analysis (ie, at the end of the Randomization Phase) will continue to receive study treatment in 21-day cycles. Tumor assessments will be performed according to the local standard of care, and scans will no longer be required to be sent to the ICL. The Off-Treatment Visit will occur within 30 days after the final dose of study treatment.

The **Follow-up Period**, which will begin the day after the Off-Treatment Visit and will continue as long as the study subject is alive, unless the subject withdraws consent, is lost to follow-up, or the sponsor terminates the study. 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.

Subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1 week) for PFS2, survival, and all subsequent anticancer treatments received. This information will be recorded unless this information is not allowed to be provided due to confidentiality. The sponsor may decide to terminate survival follow-up after the completion of the primary study analysis. All AEs will be captured for up to 30 days after last dose of study drug. SAEs must be collected through 120 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of the last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to study drug through breastfeeding during study treatment or within 120 days of the last study treatment, or 30 days following the last study treatment if the subject initiates a new anticancer therapy, whichever is earlier, must be reported.

The definition of the end of the study is the date of the data cutoff for the final overall survival analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later.

Number of Subjects

Approximately 1050 subjects will be randomized (350 subjects in each treatment arm).

Inclusion Criteria

1. Histological or cytological confirmation of RCC with a clear-cell component (original tissue diagnosis of RCC is acceptable).
2. Documented evidence of advanced RCC.
3. 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.
4. Male or female subjects age ≥18 years (or any age greater than 18 years of age if that age is considered to be an adult per the local jurisdiction) at the time of informed consent
5. Karnofsky Performance Status (KPS) of ≥70.

6. 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.
7. Adequate renal function defined as creatinine ≤1.5× upper limit of normal (ULN); or for subjects with creatinine >1.5×ULN, the calculated creatinine clearance ≥30 mL/min (per the Cockcroft-Gault formula) is acceptable.
8. Adequate bone marrow function defined by:
   - Absolute neutrophil count (ANC) ≥1500/mm^3
   - Platelets ≥100,000/mm^3
   - Hemoglobin ≥9 g/dL
     NOTE: Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within the previous 2 weeks.
9. Adequate blood coagulation function defined by International Normalized ratio (INR) ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR is within therapeutic range of intended use of anticoagulants.
10. Adequate liver function defined by:
    - Total bilirubin ≤1.5×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), unless there are bone metastases. Subjects with ALP values >3×ULN and known to have bone metastases can be included.
11. Provide written informed consent.
12. Willing and able to comply with all aspects of the protocol.

Exclusion Criteria

1. Subjects who have received any systemic anticancer therapy for RCC, including anti-VEGF therapy, or any systemic investigational anticancer agent. Prior adjuvant treatment with an investigational anticancer agent is not allowed unless the investigator can provide evidence of subject's randomization to placebo arm.
2. Subjects with CNS metastases are not eligible unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment.
3. Active malignancy (except for RCC, definitively treated basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix or bladder) within the past 24 months. Subjects with history of localized & low risk prostate cancer are allowed in the study if they were treated with curative intent and there is no PSA recurrence within the past 5 years.
4. 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.
5. Subjects who are using other investigational agents or who had received investigational drugs ≤4 weeks prior to study treatment start.

6. Received a live vaccine within 30 days of planned start of study treatment (Cycle 1/Day 1). Examples of live vaccines include, but are not limited to, measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
7. Subjects with proteinuria >1+ on urine dipstick testing 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×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×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, everolimus, and/or sunitinib.
13. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels 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 12 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, cerebrovascular accident (CVA), or cardiac arrhythmia associated with hemodynamic instability.
    The following is also excluded:
    - Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by MUGA or echocardiogram.
16. Active infection (any infection requiring systemic treatment).
17. Subjects known to be positive for Human Immunodeficiency Virus (HIV).
18. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).
19. Known history of, or any evidence of, interstitial lung disease
20. Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
21. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
22. Subjects with a diagnosis of immunodeficiency or who are receiving chronic systemic steroid therapy (at doses exceeding 10 mg/day of prednisone or equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. Physiologic doses of corticosteroids (up to 10 mg/day of prednisone or equivalent) may be used during the study.

23. Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
24. 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.
25. Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 120 days after study 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.
26. Males who have not had a successful vasectomy (confirmed azoospermia) and do not agree to use condom + spermicide OR have a female partner who does not meet the criteria above (ie, is of childbearing potential and not practicing highly effective contraception throughout the study period), starting with the first dose of study therapy through 120 days after the last dose of study therapy, unless sexually abstinent. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
27. Known intolerance to any of the study drugs (or any of the excipients).
28. Subject has had an allogenic tissue/solid organ transplant.

Study Treatments

Test Arm (Arm A): Lenvatinib is provided as 4-mg and 10-mg capsules. Everolimus is provided as 5-mg tablets. Lenvatinib 18 mg (one 10-mg plus two 4-mg capsules) plus everolimus 5 mg will be taken orally once daily in each 21-day cycle.

Test Arm (Arm B): Lenvatinib is provided as 4-mg and 10-mg capsules. Lenvatinib 20 mg (two 10-mg capsules) once daily will be taken orally in each 21-day cycle.

Pembrolizumab is provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab. Pembrolizumab will be administered at a dose of 200 mg IV over 30 minutes on Day 1 of each 21-day cycle.

Comparator Arm (Arm C): Sunitinib malate will be provided as 12.5-mg and 25-mg capsules. Sunitinib 50 mg once daily will be administered orally for 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) in each 21-day cycle.

Dose Modifications

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

Lenvatinib-Everolimus Combination

Dose reduction and interruptions for subjects who experience lenvatinib-everolimus combination therapy-related toxicity will be managed as described in the table below. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.

The starting dose of lenvatinib is 18 mg/day for subjects enrolled in Arm A. Lenvatinib dose reductions occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the sponsor.

Once the study drug dose has been reduced, it 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.

Refer to the subsections below for management of hypertension, proteinuria, diarrhea, non-infectious pneumonitis, infections, blood glucose/ lipids, hepatotoxicity, thromboembolic events and posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS), hypocalcemia, and hemorrhage, as appropriate, before 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 to 14 mg once a day (1-level reduction) and resume everolimus at the same dose as prior to dose interruption

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

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib and everolimus until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction). 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 to 8 mg orally once a day (1-level reduction). 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	Discuss with sponsor
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 and/or diarrhea prior to any study treatment interruption or dose reduction.
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 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 1 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-Pembrolizumab Combination

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in the table below. Investigators will decide the probability of the event being related to one of both drugs as to whether dose modification of one or both drugs is required.

The starting dose of lenvatinib is 20 mg/day for subjects enrolled in Arm B. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the sponsor. Once the study drug dose has been

reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the sponsor's approval is required to increase the dose.

Refer to the subsections below for management of hypertension, proteinuria, diarrhea, hepatotoxicity, thromboembolic events, PRES/RPLS, hypocalcemia, and hemorrhage, as appropriate, before consulting the dose modification table below.

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs are reversible and can be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in the *Dose Modification Guidelines for Pembrolizumab-Related Adverse Events* table below. See Table 4, *Infusion Reaction Treatment Guidelines,* for supportive care guidelines, including premedications.

Dose Modification Guidelines for Lenvatinib-Related Adverse Events (for the Lenvatinib-Pembrolizumab Combination Arm)

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with sponsor
Grade 4[f]: 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 and/or diarrhea prior to any lenvatinib interruption or dose reduction.

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

Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitor and Follow-up
General instructions: Corticosteroid taper should be initiated upon AE improving to Grade 0 or 1 and continue to taper over at least 4 weeks. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has improved to Grade 0 or 1 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. **For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.**				
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper Subjects with diarrhea/ colitis should be advised to drink	Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie,
	Grade 4	Permanently discontinue		

			liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.	peritoneal signs and ileus) Subjects with Grade ≥2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis
AST[a] / ALT[a] elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for subjects with T1DM . Administer anti-hyperglycemic in subjects with hyperglycemia.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue		

Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other irAEs	Intolerable/ persistent Grade 2	Withhold		
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician.

For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when the AE improves to Grade ≤2 and is controlled with hormonal replacement therapy or metabolic control is achieved (in the case of T1DM).

GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; T1DM = Type 1 diabetes mellitus.

a: If a subject with liver metastasis has Grade 2 AST or ALT at the start of study treatment, and the AST or ALT value increases by ≥50% relative to Baseline and lasts for ≥1 week, then the subject should permanently discontinue study treatment.

Sunitinib

The starting dose of sunitinib is 50 mg/day on a Schedule 4/2 for subjects enrolled in Arm C. See drug-drug interactions section in protocol for dose recommendations if sunitinib must be co-administered with a strong CYP3A4 inhibitor or inducer.

Dose reduction and interruptions for subjects who experience sunitinib therapy-related toxicity will be managed as described in the table below. Sunitinib dose reductions occur in succession based on the previous dose level (37.5, 25 mg/day schedule 4/2). Any dose reduction below 25 mg/day must be discussed with the sponsor. Once the study drug dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the sponsor's approval is required to increase the dose.

Refer to the subsections below for management of hypertension, proteinuria, diarrhea, hepatotoxicity, thromboembolic events, PRES/RPLS, and hemorrhage, as appropriate, before consulting the dose modification table below.

Dose Modification Guidelines for Sunitinib-related Toxicity

Treatment-Related Toxicity[a,b]	During Therapy	Adjusted Dose
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e]		
First occurrence	Interrupt sunitinib until resolved to Grade 0-1, or tolerable Grade 2	37.5 mg daily for 4 weeks followed by 2 weeks off (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt sunitinib until resolved to Grade 0-1, or tolerable Grade 2	25 mg daily for 4 weeks followed by 2 weeks off (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt sunitinib	Discuss with sponsor
Grade 4[f]: 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 and/or diarrhea prior to any study treatment interruption or dose reduction.

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 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 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.

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

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/sunitinib have BP of ≤150/90 mm Hg 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/sunitinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Procedures/ Assessments. Hypertension will be graded using CTCAE v4.03, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's initial BP measurement is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as one BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. 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 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

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

Subjects with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles.
A diary will be provided to the subject to capture the blood pressure evaluations between study visits.

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

1. Continue study drug 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/sunitinib administration should be interrupted and 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/sunitinib administration should be interrupted and 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/sunitinib administration should be interrupted and 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 drug

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:

Grading of Proteinuria

- Grading of proteinuria according to CTCAE v4.03 will be based on the 24-hour urinary protein result if available.

Management of Proteinuria

- Management of lenvatinib/sunitinib administration will be based on the grade of proteinuria according to the respective treatment arm's Dose Modification Guidelines.
- In the event of nephrotic syndrome, lenvatinib/sunitinib must be discontinued

Detection and Confirmation

1. Perform urine dipstick testing per the Schedule of Assessments (Table 7 and Table 8)
2. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) or an immediate spot urine protein-to-creatinine ratio (UPCR) test 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/sunitinib dose level
    - When there has been a lenvatinib/sunitinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+

3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Monitoring

- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

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 respective treatment arm's Dose Modification Guidelines 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, 2016). 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.

1. 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).
2. 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).
3. If symptoms are life-threatening (CTCAE Grade 4):
   - Study medications should be discontinued.

MANAGEMENT OF INFECTIONS

Everolimus has immunosuppressive properties and may predispose subjects to infections. It is important therefore 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 (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the Schedule of Procedures/Assessments and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in the respective treatment arm's Dose Modification Guidelines 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, 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 respective treatment arm's Dose Modification Guidelines 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)

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, the respective treatment arm's Dose Modification Guidelines 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.

MANAGEMENT OF HEMORRHAGE

Dose modification guidelines for lenvatinib- (Arms A and B) and sunitinib- (Arm C) related adverse events should be followed for the management of hemorrhage. Either resume lenvatinib/sunitinib at a reduced dose or discontinue lenvatinib/sunitinib, depending on the severity and persistence of hemorrhage.

For subjects receiving treatment with sunitinib (Arm C) who experience hemorrhage associated with thrombocytopenia, treatment interruption is recommended; following resolution, treatment may be resumed at the discretion of the investigator.

Duration of Treatment

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

- Progressive Disease (PD) (as confirmed by independent review)

  Note: Subjects will be permitted to continue treatment beyond initial RECIST 1.1-defined progression as long as investigator-assessed clinical benefit is observed and the subject is tolerating study drug. Subjects will discontinue study treatment upon evidence of further progression and/or loss of clinical benefit as judged by the Investigator.
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Completion of 35 treatments (approximately 2 years) with pembrolizumab
- Termination of the study by the Sponsor

The duration of treatment for each subject is estimated to be approximately 15 months.

Concomitant Drug/Therapy

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.

The following concomitant therapies are also **allowed**:

- Thyroid hormone suppressive therapy
- Adjuvant hormonal therapy for history of definitively treated breast or prostate cancer
- Anticoagulants including low molecular weight heparin (LMWH), warfarin, anti-Xa agents
- Antiinflammatory agents
- Bisphosphonates or denosumab
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the subject is enrolled)
- Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases will be permitted without being considered PD

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

- For minor procedures: stop lenvatinib 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 investigator and the sponsor.

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

- Concurrent anticancer therapies such as chemotherapy, TKIs, radiotherapy (with the exception of palliative radiotherapy as specified above), antitumor interventions (surgical resection, surgical debulking of tumors, etc.), or cancer immunotherapy
- Concurrent other investigational drugs
- For subjects in Arms A and B, live vaccines while participating in the study. Examples of live vaccines include, but are not limited to 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, FluMist®) are live attenuated vaccines, and are not allowed.

  For subjects in the lenvatinib plus pembrolizumab arm (Arm B), systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. Physiologic doses of corticosteroids (up to 10 mg/day of prednisone or equivalent) may be used during the study. Note: Use of prophylactic corticosteroids to prevent allergic reactions (eg, intravenous [IV] contrast dye or transfusions) is permitted. Inhaled steroids are allowed for management of asthma or seasonal allergies.

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

Assessments

Efficacy Assessments

Tumor assessments will be performed using RECIST 1.1 (for all subjects). 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 efficacy assessment. Tumor assessments will be carried out following the guidelines provided by the ICL. Historical CT or MRI scans performed within 28 days before randomization, but before the signing of informed consent, may be used as screening scans to demonstrate eligibility, provided they meet minimum standards as separately defined by the ICL.

Tumor assessments will be performed during the Prerandomization Phase and then every 8 weeks from the date of randomization during treatment cycles in the Randomization Phase and as determined by the treating physician in the Extension Phase. A bone scan will be performed within 6 weeks prior to randomization (historical is acceptable), every 24 weeks after randomization and during Follow-up, and within a target of 1 week but no more than 2 weeks following a CR as assessed by the investigator.

A brain scan (CT of the brain with contrast or MRI of the brain pre- and post-gadolinium) 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 CR. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment time points (eg, every 8 weeks).

All subjects will be permitted to continue treatment beyond initial RECIST 1.1-defined progression as long as the investigator believes that the subject is still receiving clinical benefit and is tolerating study drug treatment.

Clinical benefit is defined as:

- Absence of signs and symptoms of PD (including labs)
- No decline in performance status
- Absence of rapid progression of disease
- Absence of progressive tumor(s) at critical sites requiring urgent intervention (eg, spinal cord compression).

These subjects must continue tumor assessments at the same interval and have copies of all tumor assessments sent to the ICL until further progression and/or loss of clinical benefit, as judged by the investigator. The assessment of clinical benefit should take into account the potential efficacy benefit versus the safety risk of continuation of treatment. All decisions to continue treatment beyond initial progression determined by the investigator will need to be discussed with the Eisai Medical Monitor.

During the Randomization Phase, disease progression (per RECIST 1.1) must be confirmed by independent review by the ICL prior to the investigator discontinuing study treatment for a subject.

In situations where the investigator judges that alternative treatments must be instituted immediately for management of urgent medical complications of disease progression, study drug may be discontinued without waiting for independent confirmation of radiographic evidence of disease progression. Subjects who discontinue study treatment without disease progression in the Randomization Phase will continue to undergo tumor assessments every 8 weeks and a bone scan every 24 weeks in the Follow-up Period, until disease progression is documented or another anticancer therapy is initiated. Subjects who have discontinued study treatment without tumor progression in the Extension Phase will have tumor assessments performed as clinically indicated using the investigator's discretion, following the prevailing local standard of care, but not less frequently than every 12 weeks. Copies of tumor assessment scans will no longer be sent to ICL and independent review will not be carried out during the Extension Phase.

Pharmacokinetic Assessments

Blood samples will be collected from all subjects in Arms A and B. Plasma concentrations of lenvatinib (for subjects in Arms A and B), whole blood concentrations of everolimus (for subjects in Arm A only), and serum concentrations of pembrolizumab (for subjects in Arm B only) will be measured. Data for lenvatinib and everolimus will be analyzed using a population PK approach, while pembrolizumab data will be compared with historical data. Serum antidrug antibodies (ADA) and neutralizing antibodies (NAb) to pembrolizumab will be measured for subjects in Arm B.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood and Tissue Biomarkers: Blood samples for the development of exploratory predictive biomarkers will be collected before the first dose of study drug, on Cycle 1 Day 15, and on Day 1 of subsequent cycles (during Treatment / Randomization Phase), and at the off-treatment assessment from all enrolled subjects across the three treatment arms. Biomarker discovery and/or validation may be performed to identify blood or tumor biomarkers that may be useful to predict subject response to study drug, evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Blood samples may undergo global proteomic and/or enzyme-linked immunosorbent assay (ELISA)-based analyses or multiplex bead-based immunoassay, but not limited to, in an effort to identify protein biomarkers. Potential target engagement and pharmacodynamic markers include VEGF, FGF23 and other relevant FGF ligands, Ang-2/Tie-2, and other relevant circulating markers. In addition, biomarkers identified in other clinical studies of study drug may also be assessed in samples collected from subjects

enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Pharmacokinetic-Pharmacodynamic

Data from Arms A and B of the study will be used to explore PK/pharmacodynamic relationships for effects of lenvatinib in combination with pembrolizumab or everolimus on PFS, other efficacy-related parameters including ORR and OS, AEs/dose reductions, and blood and tissue biomarkers. Exploratory/graphical analyses will be conducted for PK/pharmacodynamic evaluations and, if possible, will be followed by model-based analyses.

Pharmacogenetic/Pharmacogenomic (PG) Assessments

Archived, fixed tumor tissue from the most recent surgery or biopsy will be collected (if available) from all enrolled subjects across the three treatment arms for potential assessment of mutations and other genetic alterations or genes and/or proteins that may be important in the development and progression of cancer as well as in response to study drug treatment for potential use in diagnostic development. Genetic alterations in selected molecular targets may be explored based on their potential involvement in renal cell tumor biology (eg, VHL, PI3K-mTOR signaling pathway genes, FGF/FGFR signaling pathway genes, HGF/cMET axis, and/or any known epigenetic modifications). Immune cell profiling and molecular targets and factors involved in immune check-point axis, such as PD1 or PD-L1 levels, markers of Th1/Th2 phenotype, and inflammatory status, may also be explored. Appropriate technology/methodologies will be used based on the amount of tumor tissue available.

A blood plasma sample to isolate circulating cell free nucleic acids and a whole blood sample for immune response profiling will be collected before the first dose of study drug, on Cycle 1 Day 15, and on Day 1 of subsequent cycles (during Treatment / Randomization Phase), and at the off-treatment assessment from all enrolled subjects across the three treatment arms. Cell free nucleic acid isolated from plasma samples may be used to explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor and to assess the immune response.

A blood sample will be collected for potential PG analysis from all enrolled subjects in treatment arms A and B (in accordance with regional or local laws). Variation in lenvatinib exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data.

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

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

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs) using CTCAE v4.03; regular laboratory evaluation for hematology, blood chemistry, and urine values; regular performance of physical examinations, periodic measurement of vital signs, ECGs and MUGA or echocardiogram.

Other Assessments

HRQoL will be assessed at Baseline (prior to first dose of study drug), on Day 1 of each subsequent cycle, at time of withdrawal, 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 FKSI-DRS, the EORTC QLQ-C30, and the EuroQOL EQ-5D-3L 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 three 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.

Bioanalytical Methods

Lenvatinib and everolimus will be quantified by use of validated High Performance Liquid Chromatography-tandem mass spectroscopy methods. Serum concentrations of pembrolizumab will be measured using validated methods.

Statistical Methods

Primary Endpoint

- **Progression-free survival (PFS)** by independent review is defined as the time from the date of randomization to the date of the first documentation of disease progression or death (whichever occurs first) as determined by IIR using RECIST 1.1. PFS censoring rules will follow the FDA guidance of 2007; specifics of this will be detailed in the Statistical Analysis Plan.

Secondary Endpoints

- **Objective response rate (ORR)** is defined as the proportion of subjects who have best overall response of CR or PR as determined by IIR using RECIST 1.1.
- **Overall survival (OS)** is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cut-off will be censored at the date the subject was last known alive, or date of data cut-off, whichever occurs first.
- **Safety** will be assessed summarizing the incidence of treatment-emergent adverse events (TEAEs) and SAEs together with all other safety parameters.
- **Proportion of subjects who discontinued treatment due to toxicity** is defined as the proportion of subjects who discontinue study treatment due to treatment-emergent adverse events (TEAEs).

- **Time to treatment failure due to toxicity** is defined as the time from the date of first dose to the date that a subject discontinues study treatment due to TEAEs.
- **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.
- **PFS on next-line of therapy (PFS2)** is defined as the time from randomization to disease progression on next-line of treatment, or death from any cause, (whichever occurs first).
- **Progression-free survival (PFS) by investigator assessment** is defined as the time from the date of randomization to the date of first documentation of disease progression based on the investigator assessment per RECIST v.1.1 or death (whichever occurs first).
- **Model-predicted clearance and AUC** for lenvatinib in Arms A and B.
- **Model-predicted clearance and AUC** for everolimus in Arm A.

Exploratory Endpoints

- **Duration of response (DOR)** is defined as the time from the date a response was first documented until the date of the first documentation of disease progression or date of death from any case.
- **Disease control rate** is the proportion of subjects who have best overall response of CR or PR or SD. Stable disease must be achieved at ≥7 weeks after randomization to be considered best overall response.
- **Clinical benefit rate** is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥ 23 weeks after randomization).
- **Blood and tumor biomarkers** will be assessed for identifying potential correlation with clinical outcomes-related endpoints.

Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT] Population) is the group of all randomized subjects regardless the treatment actually received. This is the primary analysis population used for all efficacy analyses which will be based on the intent-to-treat principle.

The Per Protocol Analysis Set is the group of those 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 assessments. Subjects for whom death occurred prior to the first post-baseline tumor assessment will also be included. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug. This is the analyses population used for all safety analyses which will be based on as-treated principle.

Population Pharmacokinetic (PK) Analysis Set: All subjects who have received at least 1 dose of study treatment with documented dosing history in the lenvatinib plus everolimus arm (Arm A) or the lenvatinib plus pembrolizumab arm (Arm B), and have measurable plasma levels of lenvatinib or whole blood levels of everolimus.

Pembrolizumab Pharmacokinetic (PK) Analysis Set: All the subjects who have received at least 1 dose of study treatment with documented dosing history in the lenvatinib plus pembrolizumab arm (Arm B) and have measurable serum concentrations of pembrolizumab.

The Pharmacodynamic Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data to derive at least 1 pharmacodynamic measurement and with documented dosing history.

The QOL Analysis Set will consist of all subjects who have any QOL data.

Efficacy Analyses

Efficacy analyses will be based on the Full Analysis Set.

Primary Analysis

The primary analysis of PFS will be based upon data provided by IIR of tumor assessments. PFS will be evaluated using Kaplan-Meier (K-M) estimates and statistical significance of difference in PFS comparing lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and lenvatinib + pembrolizumab (Arm B) vs. sunitinib alone (Arm C) will be tested by stratified logrank test with geographic region (Western Europe and North America vs. Other) and MSKCC prognostic groups (favorable, intermediate and poor risk) as strata. Median PFS and 2-sided 95% CIs will be presented and the K-M estimates of PFS will be plotted over time. Cox regression model with Efron's method for handling tied results will be used to estimate the hazard ratio and its 95% CI stratified by the stratification factors as specified above.

An interim and a final analysis of PFS are planned to be performed. Lan-DeMets spending function with O'Brien-Fleming boundary will be used to control alpha levels between the interim and final analysis of PFS. The interim analysis of PFS will be performed when it is approximately 4 months after the last subject is randomized and an approximately 80% information fraction of PFS events (as determined by the IIR) in Arm B and Arm C. The final analysis of PFS will be performed when approximately 388 PFS events, as determined by the IIR, are observed between each comparison. A graphical approach will be used to control the family wise error rate (FWER) at the two-sided 0.0499 for multiple comparisons, including both PFS comparisons of Arm B vs Arm C and Arm A vs Arm C. For each comparison, a statistical significance can be claimed based on either interim or final analysis of PFS at specified alpha levels.

Secondary Analyses

The primary endpoint PFS and key secondary endpoints, ORR and OS, will be tested using a graphical approach to control the overall FWER.

Overall Survival (OS) will be compared between lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and lenvatinib + pembrolizumab (Arm B) vs. sunitinib alone (Arm C) using the stratified logrank test with geographic region (Western Europe and North America vs. Other) and Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic groups (favorable, intermediate and poor risk) as strata. The hazard ratio and its 95% CI comparing lenvatinib + everolimus (Arm A) versus sunitinib alone (Arm C) and lenvatinib + pembrolizumab (Arm B) versus sunitinib alone (Arm C) will be estimated by a stratified Cox proportional hazards model with Efron's method for handling tied results stratified by geographic region and MSKCC prognostic groups. Median OS with 2-sided 95% CIs will be calculated using K-M product-limit estimates for each treatment arm and K-M estimates of OS will be plotted over time.

Three interim and a final analyses of OS are planned to be performed (Section 9.7.3). Lan-DeMets spending function with Pocock boundary will be used to control alpha levels among the interim and final analysis of OS. The first two OS interim analyses will be performed at the time of PFS interim and final analysis, corresponding to approximately 45% and 60% of information fractions of OS events. The third OS interim analysis will be performed at approximately 80% information fraction of OS events. The final analysis of OS will be performed when 304 OS events are observed for each comparison.

Objective Response Rate (ORR) will be calculated with exact 95% confidence intervals using the method of Clopper and Pearson. The difference between treatment arms will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by geographic region and MSKCC prognostic groups. The p-value for hypothesis testing of ORR will be based on the ORR data at the time of

the PFS interim analysis. The ORR data available at the subsequent analysis time points will be provided for supportive purposes.

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 EMA 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.

PFS2 will be calculated using the Kaplan-Meier (KM) product-limit estimates for each treatment group and presented with two-sided 95% CIs. The KM estimate of PFS2 will also be plotted over time for each treatment group.

PFS by investigator assessment per RECIST v1.1 will be analyzed similarly as for the primary endpoint of PFS by IIR per RECIST v1.1.

Pharmacokinetic Analyses

Plasma concentrations of lenvatinib and whole blood concentrations of everolimus versus time data will be analyzed using a population PK approach to estimate population PK parameters for each respective drug, while pembrolizumab concentrations will be compared graphically with historical data. For lenvatinib, data from this study will be pooled with historical data from other Phase 1 and 2 studies. For everolimus, data from this study will be pooled with data from Study E7080-G000-205.

Pharmacokinetic-Pharmacodynamic Analyses

The effect of lenvatinib in combination with everolimus or pembrolizumab on soluble, tissue, genetic and/or imaging biomarkers will be summarized using descriptive statistics using the PK/pharmacodynamic analysis set. PK/pharmacodynamic relationships (ie, exposure-efficacy, exposure-safety, and exposure-biomarker relationships) will be modeled, if possible, using a mechanistic approach, for effects of study treatment. Efficacy endpoints will include primary endpoint of PFS and other efficacy-related metrics including but not limited to ORR (based on RECIST 1.1) and OS. Safety endpoint will be most frequent AEs of special interest and dose reductions. Exploratory/graphical analyses will be conducted for PK/pharmacodynamic evaluations, and, if possible, will be followed by model-based analyses.

The PK and PK/PD analyses will be detailed in a separate analysis plan and the results will be provided in a stand-alone report.

Exploratory Analyses

Disease Control Rate and CBR will be calculated with exact 95% confidence intervals using the method of Clopper and Pearson. The differences and odds ratios of the above rates between treatment arms and corresponding two-sided 95% CIs will be calculated respectively. Median DOR among responders for each treatment arm will be presented along with its corresponding 2-sided 95% CIs. The difference in PFS between lenvatinib in combination with everolimus versus lenvatinib in combination with pembrolizumab will be analyzed using the method used for analysis of the primary endpoint.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Soluble, tissue, genetic and/or imaging biomarkers (baseline and/or post-treatment) may be summarized using descriptive statistics and correlated with clinical outcomes-related endpoints for safety and/or efficacy (including best overall response, PFS and OS) as appropriate. Details may be included in a separate analysis plan.

Safety Analyses

Safety analyses will be based on the Safety Analysis Set. All safety analyses will be summarized by treatment arm. Adverse events and serious adverse events, laboratory test results, vital signs, and echocardiogram results (including LVEF) will be summarized. Safety data will be summarized using descriptive statistics. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using n (number of subjects with available data), mean, standard deviation, median, Q1, Q3, and range (minimum and maximum) unless otherwise specified.

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

Multiplicity Adjustment

The primary endpoint, PFS, and key secondary endpoints, ORR and OS, will be tested using a graphical approach (Maurer and Bretz, 2013) to control the overall FWER.

No multiplicity adjustment will be made for testing other secondary and exploratory endpoints.

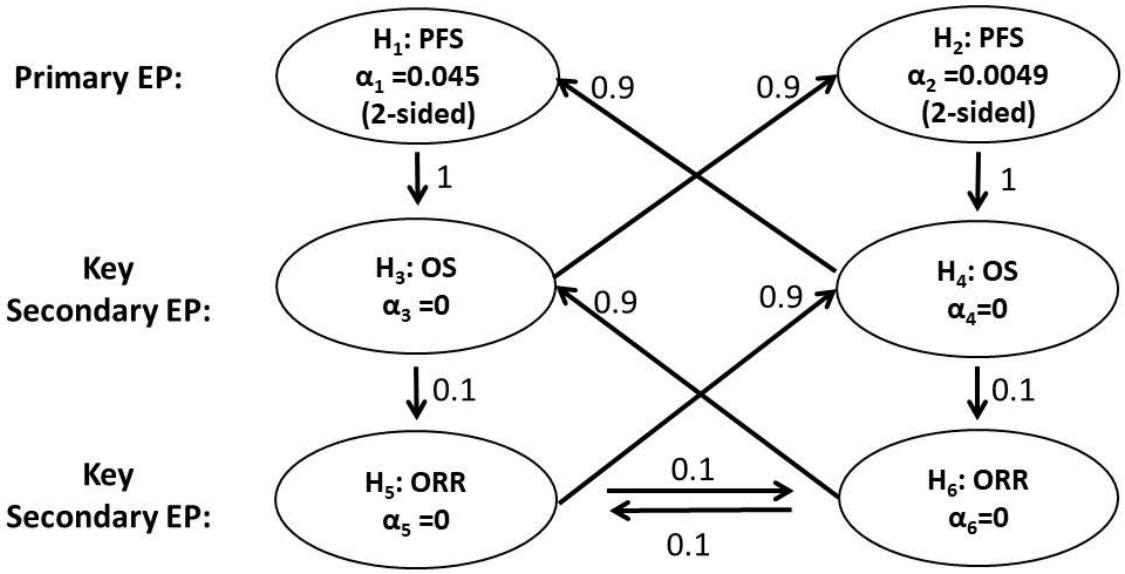

Figure: Graphical Approach to Control FWER for Testing Primary and Key Seconday Endpoints

EP = endpoint; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Hypothesis (H_1): The PFS of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_2): The PFS of lenvatinib + everolimus arm is superior to that of sunitinib arm.
Hypothesis (H_3): The OS of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_4): The OS of lenvatinib + everolimus is superior to that of sunitinib arm.
Hypothesis (H_5): The ORR of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_6): The ORR of lenvatinib + everolimus is superior to that of sunitinib arm.

Interim Analyses

An interim analysis of ORR for the first 88 subjects from the lenvatinib + pembrolizumab arm (Arm B) of this study will be performed. No comparative analysis will be conducted for the interim analysis of ORR; however, an α of 0.0001 will be allocated. This interim analysis of ORR will occur after the first 88 subjects treated in Arm B have completed a median follow-up of 12 months and a minimum duration of response follow-up of 6 months.

An interim analysis of PFS is planned to be performed. The interim analysis of PFS will be performed when it is approximately 4 months after the last subject is randomized and approximately 80% information fraction of PFS events (as determined by the IIR) in Arm B and Arm C. Lan-DeMets spending function with O'Brien-Fleming boundary will be used to control alpha levels between the interim and final analysis of PFS.

Three interim analyses of OS are planned to be performed. The first two OS interim analyses will be performed at the time of PFS interim and final analysis, corresponding to approximately 45% and 60% of information fractions of OS events. The third OS interim analysis will be performed at approximately 80% information fraction of OS events. Lan-DeMets spending function with Pocock boundary will be used to control alpha levels among the interim and final analysis of OS.

The interim efficacy analyses will be conducted by an independent statistical group that has no other responsibilities for the study.

The safety monitoring will be conducted by the independent data monitoring committee (DMC) and only the DMC will have access to data with treatment information. The frequency of the safety reviews will be defined in the DMC charter. Minutes from the open meetings of the DMC will be provided if requested by regulatory agencies. The recommendation whether to stop the trial for safety will be reached by the DMC based on their review of safety data with treatment information. The function and membership of the DMC will be described in the DMC charter.

Sample Size Rationale

The sample size is estimated based on the primary endpoint PFS. Approximately 1050 subjects will be randomized in a 1:1:1 ratio into 1 of 3 treatment arms: lenvatinib + everolimus, lenvatinib + pembrolizumab, or sunitinib alone. The randomization scheme will be stratified by geographic region (Western Europe and North America vs. Other) and MSKCC prognostic groups (favorable, intermediate and poor risk).

The same treatment effect is assumed for the primary comparisons of lenvatinib + everolimus (Arm A) and lenvatinib + pembrolizumab (Arm B) each compared to sunitinib alone (Arm C). Assuming the median PFS in sunitinib alone (Arm C) to be 12.3 months and a hazard ratio of 0.714 for the primary comparisons, this corresponds to 40% improvement (4.9 months) in median PFS from 12.3 months to 17.2 months from Arm A versus Arm C and for Arm B versus Arm C. The yearly loss to PFS event rate of 22% is assumed in the sample size calculation.

Since the study is testing more than one comparison for the primary and secondary endpoints, respectively, the graphical approach (Section 9.7.4) will be used for testing multiple hypotheses. For the two PFS comparisons (one for each test arm), the sponsor chooses to split the total alpha of 0.0499 (2-sided), as initial allocations, into $\alpha = 0.045$ for the comparison between Arm B and Arm C, and $\alpha = 0.0049$ for the comparison between Arm A and Arm C.

The study is designed to achieve 90% power at $\alpha = 0.045$ to detect a statistically significant difference in PFS in the comparison between Arm B and Arm C. Therefore, a total of 388 PFS events are required between Arms B and C in the final PFS analysis. Since the same number of PFS events are expected to be observed in Arms A and C, a total of 388 PFS events is expected in the final PFS analysis for the comparison between Arms A and C. The power to detect a statistically significant difference in PFS between Arm A and Arm C is approximately 70% at the initial assigned $\alpha = 0.0049$, and will be at least 90% when the hypothesis tests of PFS and OS in the

comparison of Arm B and Arm C are statistically significant. In the power calculation for PFS analysis, it is assumed that one interim analysis of PFS is to be performed at the 80% information fraction and a Lan-DeMets spending function with O'Brien-Fleming boundary is used between the interim and final analysis of PFS.

Assuming an average enrollment rate of 31 subjects per month, the interim and final analysis of PFS will occur approximately 38 and 45 months (34 month enrollment period) after the first subject is randomized. A total of 582 PFS events are expected in 3 arms by the time of the planned final PFS analysis.

For the key secondary endpoint of OS, a total of 304 deaths for each comparison (456 death events among the 3 arms) are expected in the final OS analysis. For OS testing, when the corresponding PFS testing is statistically significant at the initial assigned alpha, the study will provide 80% power to detect a statistically significant difference at an α level of 0.045 for the comparison between Arms B and C, and 50% power at an α level of 0.0049 for the comparison between Arm A and C. By using the graphical approach, the power for the OS comparison between Arms A and C will increase to at least 80% when the OS testing between Arms B and C is significant and both PFS tests are significant. The assumptions that are used for the OS power calculations are: 1) the hazard ratio is 0.70 (median OS is 54.1 months in Arm A or Arm B and 37.9 months in Arm C), 2) interim analyses are performed at approximately 45%, 60%, and 80% information fraction of death events, 3) a Lan-DeMets spending function with Pocock boundary is used, and 4) the yearly rate for loss to follow-up is 3%. With the planned sample size and the assumptions for enrollment, the final analysis of OS is expected to occur approximately 69 months after the first subject is randomly assigned to treatment.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	adverse events
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
CBR	clinical benefit rate (CR + PR + durable SD ≥ 23 weeks)
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	curriculum vitae
CVA	cerebrovascular accident
CYP	cytochrome P
DCR	disease control rate
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
durable SD	durable stable disease
ECG	electrocardiogram
EORTC	European Organization for the Research and Treatment of Cancer

Abbreviation	Term
EuroQOL	European Quality of Life
^{18}F-NaF	^{18}F-sodium fluoride
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms
FWER	familywise error rate
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio; heart rate
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
IIR	independent imaging review
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat data set
IV	intravenous
IxRS	interactive voice and web response system
K-M	Kaplan-Meier
KPS	Karnofsky Performance Status
LLN	lower limit of normal
LLT	lower level term
LMWH	low molecular-weight heparin
LVEF	left ventricular ejection fraction
mAbs	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

Abbreviation	Term
MSKCC	Memorial Sloan-Kettering Cancer Center
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multiple-gated acquisition
NAb	neutralizing antibody(ies)
NCCN	National Comprehensive Cancer Network
NSAID	non-steroidal antiinflammatory drug
NYHA	New York Heart Association
ORR	objective response rate
P-gp	CYP3A4/P-glycoprotein
PR	partial response
pRBC	packed red blood cells
PRES/RPLS	posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome
OS	overall survival
PD	progressive disease; pharmacodynamics
PFS	progression-free survival
PFS2	progression-free survival during next-line therapy
PG	Pharmacogenomics
PI	principal investigator
PR	partial response
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
Q3W	every 3 weeks
QD	once daily
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RTK	receptor tyrosine kinase

Abbreviation	Term
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	Système International
SOC	system organ class
SOPs	standard operating procedures
TAM	tumor associated macrophage
TEAEs	treatment-emergent adverse events
TEMAV	treatment-emergent markedly abnormal laboratory values
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBRT	whole brain radiation therapy
WHO DD	World Health Organization Drug Dictionary

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 CRA[s], 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 (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.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The definition of the end of the study is the date of the data cutoff for the final analysis of overall survival or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later. 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 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 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 Pharmaceuticals, Medical devices and Other Therapeutic Products Act (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.

With regard to the pharmacogenomic (PG) assessments described in Section 9.5.1.3.2, an informed consent for collection of samples during the study for gene analysis will be prepared separately. Subjects may still participate in the study if they do not give informed consent for gene analysis.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 200 investigational sites 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 Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Renal Cell Carcinoma: Epidemiology and Current Therapeutic Options

Renal cell carcinoma (RCC), which originates within the renal cortex from the proximal renal tubular epithelium, is the most common kidney cancer, constituting 80 to 85 percent of primary renal neoplasms (Wahal and Mardi, 2014). An estimated 365,943 new cases of kidney (renal) cancer are expected to be diagnosed in 2015, and an estimated 155,520 deaths from kidney cancer are expected to occur in 2015 (GLOBOCAN 2012).

Nephrectomy is the mainstay of treatment for RCC. Surgical resection can be curative for patients presenting with localized disease, however, approximately 20-30% of RCC patients present with metastasis at the time of initial diagnosis and less than 5% of these will present with solitary metastases. Additionally, about 40% of those with clinically localized disease may develop metastatic disease following nephrectomy. Median time to relapse following nephrectomy is 15-18 months (Athar and Gentile, 2008). Once RCC has metastasized, the 5 year survival rate ranges from 5-10% (Gupta, et al., 2008). In general, the median survival for these patients is only 12 months.

The current treatment approach for patients with metastatic RCC consists of sequential administration of single-agent therapies that target either the vascular endothelial growth

factor (VEGF)/VEGF receptor (VEGFR) or mammalian target of rapamycin (mTOR) pathways (National Comprehensive Cancer Network [NCCN] Clinical Practice Guidelines in Oncology, 2016; Escudier, et al., 2014). First-line therapy consists of treatment with anti-VEGF agents, typically sunitinib or pazopanib (Motzer, et al., 2015a; Escudier, et al., 2014), however, all patients ultimately progress after therapy (Sosman, et al., 2007) and will need further treatment.

Current strategies for first-line treatment of metastatic RCC have focused on the development of new therapeutic agents, optimal sequencing, and combinations of these agents to maximize their impact on clinical outcomes. To date, however, results of combination-therapy studies (ie, temsirolimus plus bevacizumab, temsirolimus plus sunitinib, erlotinib plus bevacizumab, everolimus plus bevacizumab) have shown no advantage in progression free survival (PFS) over monotherapy with approved single agents and, in some cases, an unacceptably high degree of toxicity (Bukowski, et al., 2007; Dorff, et al., 2014; Feldman, et al., 2009; Graves, et al., 2013; Hainsworth, et al., 2010; Kanesvaran, et al., 2015; Negrier, et al., 2011; Powles, et al., 2014; Ravaud, et al., 2013). Therefore, there remains a significant unmet medical need for more effective treatment options, including possible combination therapies, with a manageable safety profile in patients with advanced RCC.

7.1.1 Preclinical Experience with the Combination of Lenvatinib with Everolimus

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

Lenvatinib is a potent multiple-receptor tyrosine kinase (RTK) inhibitor that selectively inhibits VEGF receptors (VEGFR1 [FLT1], VEGFR2 [KDR], VEGFR3 [FLT4]) in addition to other pro-angiogenic and oncogenic pathway-related RTKs, including fibroblast growth factor (FGF) receptors FGFR1-4, platelet-derived growth factor (PDGF) receptor α, KIT, and RET. Lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in human umbilical vein endothelial cell (HUVEC) models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer drugs.

In preclinical models (A498 and Caki-1), the lenvatinib plus everolimus combination demonstrated superior antiangiogenesis as well as antitumor activity compared to each single agent alone (M14026). The mechanism of action of the combination of lenvatinib and

everolimus was further investigated in cell-based nonclinical models, and it is hypothesized that the dual inhibition of the VEGF- and FGF-driven MAPK and mTOR pathways by the combination of lenvatinib plus everolimus in endothelial cells may contribute to the enhanced antiangiogenic activity of the combination treatment. In addition, the dual targeting of the mTOR-S6K-S6 pathway by the lenvatinib plus everolimus combination may contribute towards the superior antitumor activity of the combination (W-20110629).

7.1.2 Clinical Results Obtained with Combination Lenvatinib plus Everolimus

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

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

The combination significantly prolonged progression-free survival (PFS) compared with either single-agent as shown in the Kaplan-Meier curve in Figure 1:

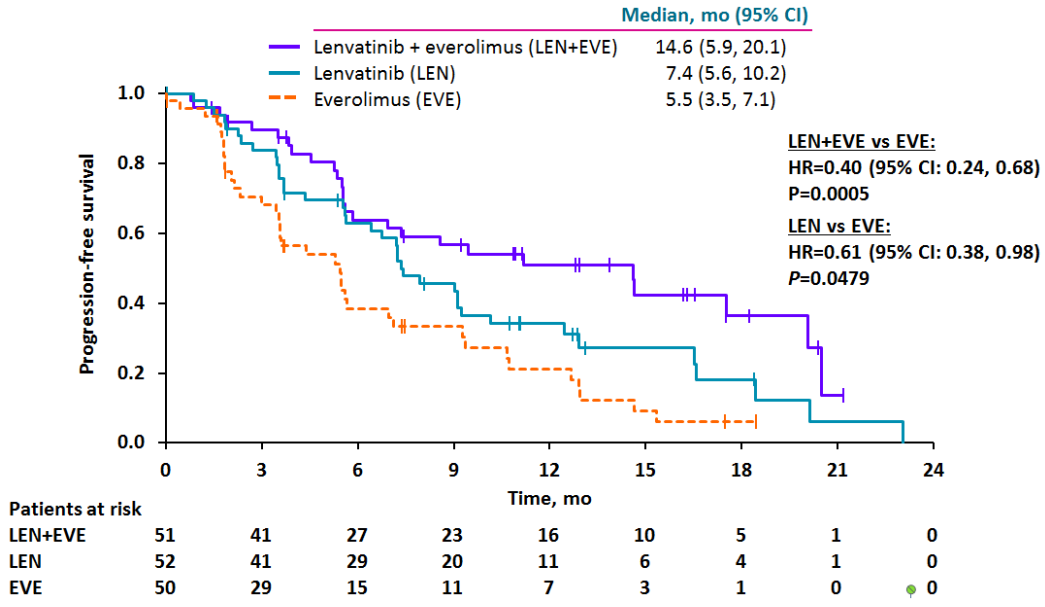

Figure 1 Kaplan-Meier Plot of Progression-free Survival – Full Analysis Set (Phase 2) – Study E7080-G000-205

CI = confidence interval; EVE = everolimus; HR = hazard ratio; LEN = lenvatinib.

Source: Study 205 CSR, Figure 4.

The safety profile for lenvatinib plus everolimus was consistent with the known toxic effects of each individual agent, with no unexpected treatment-emergent adverse events (TEAEs) observed. The most common TEAEs of any grade in the lenvatinib plus everolimus arm were diarrhea and fatigue or asthenia. Grade 3 and 4 events occurred in fewer patients allocated single-agent everolimus (25 [50%]) compared with those assigned lenvatinib alone (41 [79%]) or lenvatinib plus everolimus (36 [71%]). The most common Grade 3 or 4 TEAEs in patients allocated lenvatinib plus everolimus was diarrhea (10 [20%]), in those assigned single-agent lenvatinib it was proteinuria (10 [19%]), and in those assigned single-agent everolimus it was anemia (6 [12%]). Two deaths were deemed related to study drug, 1 cerebral hemorrhage in the lenvatinib plus everolimus group and 1 myocardial infarction with single-agent lenvatinib (Motzer, et al., 2015a).

7.1.3 Preclinical Experience with the Combination of Lenvatinib plus PD-1/L1 inhibitors

Pembrolizumab is an anti-PD-1 monoclonal antibody that releases the natural break on the immune system by blocking the interaction between the PD-1 receptor expressed on T cells and its 2 ligands, PD-L1 and PD-L2. Blockade of PD-1 or PD-L1, using monoclonal antibodies (mAbs), has demonstrated substantial clinical activity in patients with metastatic renal cell carcinoma (Brahmer, et al., 2012; Hamid and Carvajal, 2013; Philips and Atkins, 2015; Motzer, et al., 2015b).

In preclinical models, lenvatinib decreased the tumor associated macrophage (TAM) population which is known as an immune-regulator in the tumor microenvironment. By decreasing TAM, expression levels of cytokines and immune-regulating receptors were changed to increase immune activation. The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/L1 signal inhibitors. The effect of combining lenvatinib with PD-1/L1 (programmed death, ligand 1) mAbs has been investigated in the CT26 colorectal cancer syngeneic model (PD-L1 mAb) as well as the LL/2 lung cancer syngeneic model (PD-1 mAb). Combination treatment with lenvatinib and PD-1/L1 mAb showed significant and superior antitumor effects compared with either compound alone in two syngeneic models (Kato et al, 2015).

7.1.4 Preliminary Clinical Results Obtained with Combination Treatment with Lenvatinib plus Pembrolizumab

An open-label, Phase 1b/2 study (E7080-A001-111; hereafter referred to as “Study 111”) of the combination of lenvatinib plus pembrolizumab in subjects with select metastatic tumor types, including metastatic RCC is being conducted to assess the safety and efficacy of the combination of lenvatinib plus pembrolizumab. During the Phase 1b portion of the study, the recommended Phase 2 dose was determined to be 20 mg lenvatinib daily in combination with a fixed dose of pembrolizumab 200 mg given every 3 weeks, and is being used in the Phase 2 portion of the study.

As of 31 May 2017, 13 subjects (3 treated with lenvatinib 24 mg plus 200 mg pembrolizumab and 10 treated with lenvatinib 20 mg plus 200 mg pembrolizumab) were

enrolled in the Phase 1b portion of this study and 22 subjects with RCC were among those enrolled in the Phase 2 portion of this study. In Phase 1b, 8 of the 13 enrolled subjects had RCC, 2 had non-small-cell lung cancer (NSCLC), 2 had endometrial cancer, and 1 had melanoma. A total of 22 subjects were enrolled in the RCC cohort in Phase 2 of the study. Dose-limiting toxicity (DLT) reported in Phase 1b was Grade 3 arthralgia in 1 subject and Grade 3 fatigue in 1 subject, both in the 24 mg lenvatinib plus 200 mg pembrolizumab cohort. No DLT was reported in the lenvatinib 20 mg plus pembrolizumab 200 mg cohort, and this was the recommended Phase 2 dose.

Twelve of the 30 subjects (40.0%) with RCC had no prior anticancer therapy for their advanced RCC, 10 subjects (33.3%) had received 1 prior anticancer therapy, and 8 subjects (26.7%) had received 2 or more prior anticancer therapies. Of the 18 subjects (60.0%) with RCC who received prior anticancer therapy, 16 subjects received at least 1 prior VEGF-targeted therapy and 7 subjects received 2 or more prior VEGF-targeted therapies.

As of 31 May 2017, based on interim data for Phases 1b/2 combined, the best overall response for the 30 subjects with RCC at Week 24 was:

- Partial response (PR) in 19 subjects (63%)
- Stable disease (SD) in 10 subjects (33%)
- Progressive disease (PD) in 1 subject (3.3%)

The ORR (CR + PR) as determined by the investigator using immune-related RECIST (irRECIST) was 70% (95% CI: 50.6, 85.3), comprising 21 subjects with a confirmed PR. Two subjects had a confirmed PR after Week 24: 1 at Week 60 and 1 at Week 51. As of the data cutoff date (31 May 2017), the median follow-up time was 11.8 months (95% CI, 11.5, 13.7), and the median duration of objective response had not been reached.

Among the 12 subjects who were treatment-naïve, the confirmed ORR was 83.3% (95% CI: 51.6, 97.9). For the 18 subjects who received previous anticancer treatment, the ORR was 61.1% (95% CI: 35.7, 82.7).

Responses were seen in both subjects with PD-L1-positive and PD-L1 negative disease. Among the 12 subjects whose tumors expressed the PD-L1 protein, ORR was 66.7% (95% CI: 34.9, 90.1); among the 14 subjects whose tumors did not express the PD-L1 protein, ORR was 78.6% (95% CI: 49.2, 95.3).

The most frequently reported TEAEs in subjects with RCC (occurring in ≥30% of treated subjects, in descending order of frequency) were: diarrhea (n=25; 83%), fatigue (21, 70%), hypothyroidism (20, 67%), nausea (18, 60%), stomatitis (18, 60%), hypertension (16, 53%), cough (15, 50%), dysphonia (14, 47%), proteinuria (12, 40%), arthralgia (11, 37%), decreased appetite (11, 37%), epistaxis (10, 33%), vomiting (10, 33%), constipation (9, 30%), Palmar-plantar erythrodysesthesia syndrome (9, 30%), and weight decreased (9, 30%). Grade 3 TEAEs that occurred in 2 or more subjects included lipase increased (n=4, 13%), hypertension (3, 10%), proteinuria (3, 10%), amylase increased (2, 7%), dehydration (2, 7%), fatigue (2, 7%), and renal failure (2, 7%). Grade 4 TEAEs were reported for

2 subjects with RCC: lipase increased and clostridial sepsis in 1 subject each. Two subjects with RCC had a Grade 5 TEAE (malignant neoplasm progression, cerebral hemorrhage); both were considered by the investigator to be related to disease progression (PD). Serious AEs were reported for 13 subjects (43%) with RCC. Dehydration was reported as serious in 2 subjects (7%); all other SAEs occurred in 1 subject each. Treatment-emergent AEs were managed with supportive care and dose modification (treatment interruptions and dose reductions). A total of 28 subjects (93%) with RCC had a dose adjustment due to a TEAE, most commonly diarrhea (n=11, 37%) and fatigue (4, 11%). Three subjects (10%) with RCC discontinued treatment with either lenvatinib or pembrolizumab for a TEAE as the primary reason.

7.2 Study Rationale and Benefit/Risk Assessment

The currently available first-line therapies for RCC are unsatisfactory. These treatments do not induce durable tumor responses and virtually all patients experience progression of disease requiring initiation of another therapy.

Clinical evaluation of lenvatinib in combination with everolimus as a first-line therapy is warranted based on the following:

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

Clinical evaluation of combination therapy with lenvatinib plus pembrolizumab as a first-line therapy for RCC is warranted based on the following:

- Preliminary efficacy data obtained with lenvatinib in combination with pembrolizumab in Study 111 revealed that 29 (97%) of 30 subjects with RCC showed a best overall response of either PR or SD and 1 subject had PD while receiving this treatment, as described in Section 7.1.4. These efficacy data are compelling, showing significant tumor reduction with durable responses in treatment-naïve and previously treated subjects.
- Patients treated in Study 111 with the combination of lenvatinib and pembrolizumab experienced toxicities manageable with dose interruptions and dose reductions.

Therefore, based on the definitive results of Study 205 (Section 7.1.2) and the preliminary results obtained in Study 111 (Section 7.1.4), Eisai is conducting a multicenter, open-label, randomized, Phase 3 trial (Study E7080-G000-307, hereafter referred to as Study 307) to compare the efficacy and safety of lenvatinib in combination with everolimus or

pembrolizumab versus sunitinib alone in first-line treatment of subjects with advanced renal cell carcinoma.

Based on the available data to date for the two investigational treatment arms (ie, Arms A and B), the benefit/risk profile for subjects who participate in Study 307 is positive. With the measures contained within the protocol, the safety will continue to be assessed moving forward.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to demonstrate that lenvatinib in combination with everolimus (Arm A) or pembrolizumab (Arm B) is superior compared to sunitinib alone (Arm C) in improving PFS (by independent imaging review [IIR] using Response Evaluation Criteria in Solid Tumors [RECIST 1.1]) as first-line treatment in subjects with advanced renal cell carcinoma.

8.2 Secondary Objectives

- To compare objective response rate (ORR) by IIR using RECIST 1.1 of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.
- To compare overall survival (OS) of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.
- To compare safety and tolerability of treatment with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib, including the assessment of the proportion of subjects who discontinued treatment due to toxicity and time to treatment failure due to toxicity.
- To compare the impact of treatment on Health-Related Quality of Life (HRQoL) as assessed by using the Functional Assessment of Cancer Therapy Kidney Index-Disease-Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30 and the European Quality of Life (EuroQOL) EQ-5D-3L instruments, for subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.
- To assess PFS on next-line of therapy (PFS2) as reported by investigator.
- To assess PFS based on investigator assessment per RECIST v.1.1.
- To characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with everolimus or pembrolizumab.
- To compare the PK of pembrolizumab from this study to historical data.
- To characterize the population PK of everolimus when co-administered with lenvatinib.
- To assess the PK/pharmacodynamic relationship between exposure and efficacy/biomarkers/safety, if possible, using a mechanistic approach.

8.3 Exploratory Objectives

- To compare objective response rate (ORR) by investigator assessment using RECIST 1.1
- To assess the duration of response (DOR) by IIR and investigator assessment using RECIST 1.1 for subjects in all treatment arms.
- To compare the disease control rate (DCR) (complete response [CR] + PR + stable disease [SD]) and clinical benefit rate (CBR) (CR, PR + durable SD) by IIR and investigator assessment using RECIST 1.1 of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib.
- To compare PFS by IIR and investigator assessment using RECIST 1.1 in subjects treated with lenvatinib in combination with everolimus (Arm A) versus lenvatinib in combination with pembrolizumab (Arm B).
- To investigate the relationship between candidate tumor and blood biomarkers and clinical outcome measures including antitumor activity of study treatment.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a multicenter, randomized, open-label, Phase 3 study to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line treatment in subjects with advanced RCC.

Approximately 1050 eligible subjects will be randomized to 1 of the following 3 treatment arms in a 1:1:1 ratio, with approximately 350 subjects in each arm:

- Arm A: lenvatinib 18 mg (orally, once daily) plus everolimus 5 mg (orally, once daily)
- Arm B: lenvatinib 20 mg (orally, once daily) plus pembrolizumab 200 mg (intravenously [IV], every 3 weeks [Q3W])
- Arm C: sunitinib 50 mg (orally, once daily) on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2)

The study will be conducted in 3 Phases: a Pre-randomization Phase, a Randomization Phase, and an Extension Phase. The Pre-randomization phase will have 2 periods, Screening and Baseline. The Randomization Phase and the Extension Phase will each consist of 2 periods, a Treatment Period and a Follow-up Period.

The Randomization Phase of the study will end at the date of the data cutoff for the planned final analysis of PFS by independent review, which is estimated to be approximately 45 months after the first subject is randomized assuming an average enrollment rate of 31 subjects/month.

Subjects who are still on treatment at the time of the data cutoff will continue to receive study treatment in the Extension Phase. Ongoing subjects will be followed for survival and all subsequent anticancer treatments received will be recorded on the case report form (CRF).

The Sponsor may decide to terminate survival follow-up after the completion of the PFS analysis.

Eisai will closely monitor subject dropout, including refusal of assignment. In the event that the dropout rate exceeds 5%, Eisai, in collaboration with the principal investigator(s), will consider capping the enrollment in the respective site(s) and/or region. The dropout plan will be detailed in a separate document.

The definition of the end of the study is the date of the data cutoff for the final analysis of overall survival or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later.

An overview of the study design is presented in Figure 2.

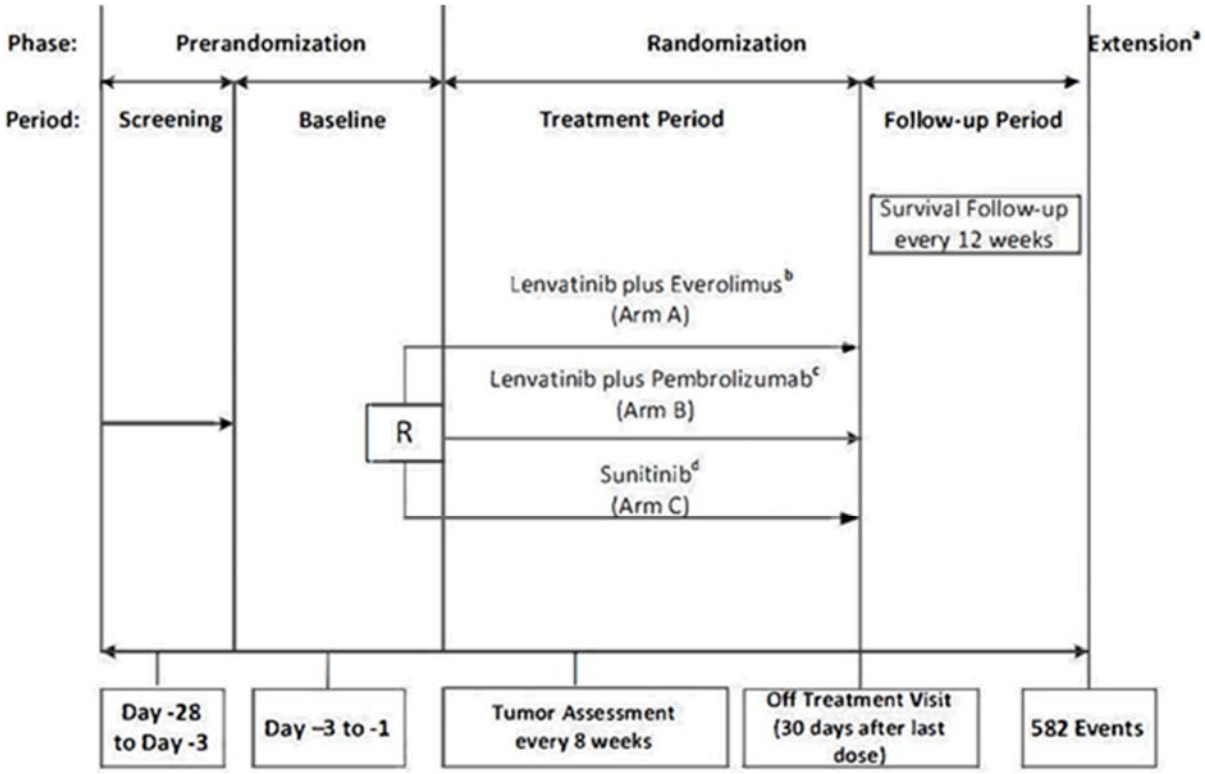

Figure 2 Study Design for Study E7080-G000-307

R = Randomization
a: Extension Phase includes a Treatment and Follow-up Period. All subjects still on treatment at the end of the Randomization Phase will enter the Extension Phase and continue to receive the same study treatment they received in the Randomization Phase.
b: Lenvatinib 18 mg plus everolimus 5 mg given orally once daily.
c: Lenvatinib 20 mg once daily plus pembrolizumab 200 mg intravenously every 3 weeks.
d: Sunitinib 50 mg once daily on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2).

9.1.1 Prerandomization/Pretreatment Phase

The Pre-randomization 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. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the sponsor. 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.

The Screening Disposition 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 assessments can be performed within 72 hours or prior to randomization on Cycle 1/Day 1. Laboratory tests and a pregnancy test (for female subjects of childbearing potential) may be performed up to 72 hours before randomization. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the sponsor.

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

9.1.2 Randomization/Treatment Phase

The Randomization Phase will begin at the time of randomization of the first subject and will end on the data cutoff date for the planned final PFS analysis, at which time all subjects who are still on study treatment or in follow-up will enter the Extension Phase. The Randomization Phase will include both a Treatment Period and Follow-up Period.

9.1.2.1 Treatment Period

The Treatment Period for each subject will begin at the time of randomization and will end with the completion of the Off-Treatment Visit, which will occur within 30 days after the final dose of study treatment. All AEs will be captured up to 30 days after last dose of study drug. Serious AEs must be collected for 120 days after the subject's last dose of study drug, or 30 days following the last dose of study drug if the subject initiates new anticancer therapy, whichever is earlier.

- Subjects will receive study treatment as continuous 21-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. Subjects will continue to receive study treatment until confirmed PD by IIR, development of unacceptable toxicity, subject request, withdrawal of consent, completion of 35 treatments (approximately 2 years) with pembrolizumab, or study termination by the sponsor.
- Subjects in Arm B who discontinue pembrolizumab after 35 treatments may continue treatment with lenvatinib alone unless any other criteria above apply.
- Discontinuation of treatment may be considered for those subjects who fulfill all of the following criteria: attain a confirmed CR, have been treated for at least 8 cycles (at least 24 weeks) with pembrolizumab, and have received at least 2 treatments with pembrolizumab beyond the date when the initial CR is declared. In the presence of clinical benefit, subjects who complete treatment with pembrolizumab may continue to receive lenvatinib alone after this time point.

Subjects will be permitted to continue study treatment beyond RECIST 1.1-defined disease progression as long as the treating investigator considers that there is clinical benefit, and the subject is tolerating study drug. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the Eisai Medical Monitor. Subjects will discontinue study treatment upon evidence of further progression and/or loss of clinical benefit as judged by the Investigator.

Disease progression (per RECIST 1.1) must be confirmed by IIR by the imaging core laboratory (ICL) prior to the investigator discontinuing study treatment for a subject. In situations where the investigator judges that alternative treatments must be instituted immediately for a subject`s safety, study drug may be discontinued without waiting for independent review confirmation of radiographic evidence of disease progression. If possible, before discontinuation of the subject from the study, the investigator should consult with the sponsor.

9.1.2.2 Follow-Up Period

The Follow-up Period will begin the day after the Off-Treatment Visit and will continue as long as the subject is alive, unless the subject withdraws consent, is lost to follow-up, or the sponsor terminates the study. 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.

During the follow-up period, subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (± 1 week) for PFS2, survival, and all subsequent anticancer treatments received. This information will be recorded unless this information is not allowed to be provided due to confidentiality. The

sponsor may choose to discontinue survival follow-up following completion of the primary study analysis when appropriate, eg, when only a minimal number of subjects remain in follow up.

If a subject becomes unavailable for follow-up (eg, misses scheduled assessment, telephone contact), the investigator or designee will make every attempt to contact the subject to determine his or her status. All attempts at contact will be recorded in the subject's medical notes. Subjects will only be deemed lost to follow-up:

- After a minimum of 3 attempted contacts (eg, telephone, letter) with the subject, the subject's family, or the primary care (family) physician, at least 4 weeks apart. The last attempt at contact must occur no earlier than 3 months after the subject's last successful contact.
- If the last attempt at contact is unsuccessful, the site should write a letter with certified proof of posting to the subject, subject's family, or the primary care (family) physician to request information on the subject's status, if regionally required.

All subjects who discontinue study treatment prior to disease progression will continue to undergo tumor assessments every 8 weeks and a bone scan every 24 weeks in the Follow-up Period, until disease progression is documented and confirmed by IIR or a new anticancer therapy is initiated, unless the subject withdraws consent or is lost to follow-up.

To ensure current and complete survival data are available at the time of analysis, updated survival status may be requested during the course of the study by the sponsor (eg, independent Data Monitoring Committee [DMC] reviews, interim analysis, final analysis). Upon notification by the sponsor, all subjects who do not or will not have a scheduled study visit or study contact during the sponsor-defined time period will be contacted by the investigator or designee for their survival status.

9.1.3 Extension Phase

9.1.3.1 Treatment Period

All subjects who are still on study treatment following the data cut-off date of the planned final PFS analysis (ie, at the end of the Randomization Phase) will continue to receive the same study treatment in 21-day cycles. Tumor assessments will be performed according to the local standard of care, but not less frequently than every 12 weeks, and scans will no longer be required to be sent to the ICL. Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, loss of clinical benefit, completion of 35 treatments (approximately 2 years) with pembrolizumab, or sponsor termination of the study. In the presence of clinical benefit, subjects in Arm B who discontinue pembrolizumab may continue treatment with lenvatinib alone unless any of the other discontinuation criteria apply.

The Off-Treatment Visit will occur within 30 days after the final dose of study treatment. All AEs will be captured up to 30 days after last dose of study drug. Serious AEs must be

collected for 120 days after the subject's last dose of study drug or 30 days following the last dose of study drug if the subject initiates new anticancer therapy, whichever is earlier.

9.1.3.2 Follow-up Period

The Follow-up Period, which will begin the day after the Off-Treatment Visit and will continue as long as the study subject is alive, unless the subject withdraws consent, is lost to follow-up, or the sponsor terminates the study. 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. See Section 9.1.2.2 for information pertaining to the circumstances under which a subject is considered "lost to follow-up."

Subjects will be treated by the investigator according to the prevailing local standard of care. Subjects will be followed every 12 weeks (±1 week) for PFS2, survival, and all subsequent anticancer treatments received. This information will be recorded unless this information is not allowed to be provided due to confidentiality. The sponsor may decide to terminate survival follow-up after the completion of the primary study analysis.

To ensure current and complete survival data are available at the time of analysis, updated survival status may be requested during the course of the study by the sponsor (eg, independent DMC reviews, interim analysis, final analysis). Upon notification by the sponsor, all subjects who do not or will not have a scheduled study visit or study contact during the sponsor-defined time period will be contacted by the investigator or designee for their survival status.

9.2 Discussion of Study Design, Including Choice of Control Groups

This multicenter, randomized, open-label, Phase 3 study was designed to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line treatment in subjects with advanced RCC. 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 arms, and to ensure the validity of statistical comparisons across treatment arms. Treatments will be open-labeled, since the dosage and administration is different between lenvatinib, everolimus, pembrolizumab and sunitinib. Sunitinib will be used as a comparator since it is a recognized standard-of-care for first-line treatment of patients with advanced RCC.

The study sample size is based on the required target events to detect a difference in at least one of the primary comparisons of PFS (combination lenvatinib plus everolimus versus sunitinib, or combination lenvatinib plus pembrolizumab versus sunitinib) in a reasonable time frame.

9.3 Selection of Study Population

Approximately 1050 subjects will be randomized at approximately 200 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

1. Histological or cytological confirmation of RCC with a clear-cell component (original tissue diagnosis of RCC is acceptable).
2. Documented evidence of advanced RCC.
3. 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 computed 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.
4. Male or female subjects age ≥18 years (or any age >18 years of age (if that age is considered to be an adult per the local jurisdiction) at the time of informed consent
5. Karnofsky Performance Status (KPS) of ≥70.
6. 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.
7. Adequate renal function defined as creatinine ≤1.5× upper limit of normal (ULN); or for subjects with creatinine >1.5×ULN, the calculated creatinine clearance ≥30 mL/min (per the Cockcroft-Gault formula) is acceptable (Appendix 12).
8. Adequate bone marrow function defined by:
   - Absolute neutrophil count (ANC) ≥1500/mm^3
   - Platelets ≥100,000/mm^3
   - Hemoglobin ≥9 g/dL

   NOTE: Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within the previous 2 weeks.
9. Adequate blood coagulation function defined by International Normalized ratio (INR ≤1.5 unless participant is receiving anticoagulant therapy, as long as INR is within therapeutic range of intended use of anticoagulants.
10. Adequate liver function defined by:
    - Total bilirubin ≤1.5×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), unless there are bone metastases. Subjects with ALP values >3×ULN and known to have bone metastases can be included.

11. Provide written informed consent.
12. Willing and able to comply with all aspects of the protocol.

9.3.2 Exclusion Criteria

1. Subjects who have received any systemic anticancer therapy for RCC, including anti-VEGF therapy, or any systemic investigational anticancer agent. Prior adjuvant treatment with an investigational anticancer agent is not allowed unless the investigator can provide evidence of subject's randomization to placebo arm.
2. Subjects with central nervous system (CNS) metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment.
3. Active malignancy (except for RCC, definitively treated basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix or bladder) within the past 24 months. Subjects with history of localized & low risk prostate cancer are allowed in the study if they were treated with curative intent and there is no PSA recurrence within the past 5 years.
4. 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.
5. Subjects who are using other investigational agents or who had received investigational drugs ≤4 weeks prior to study treatment start.
6. Received a live vaccine within 30 days of planned start of study treatment (Cycle 1/ Day 1). Examples of live vaccines include, but are not limited to, measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
7. Subjects with proteinuria >1+ on urine dipstick testing 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×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×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, everolimus, and sunitinib.
13. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels 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 12 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, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. The following is also excluded:
    - Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by MUGA or echocardiogram.
16. Active infection (any infection requiring systemic treatment).
17. Subjects known to be positive for Human Immunodeficiency Virus (HIV).
18. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).
19. Known history of, or any evidence of, interstitial lung disease.
20. Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis.
21. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in a clinical study.
22. Subjects with a diagnosis of immunodeficiency or who are receiving chronic systemic steroid therapy (doses exceeding 10 mg/day of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. Physiologic doses of corticosteroids (up to 10 mg/day of prednisone or equivalent) may be used during the study.
23. Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
24. 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.

25. Females of childbearing potential* who:
    - do not agree to use a highly effective method of contraception for the entire study period and for 120 days after study 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.
26. Males who have not had a successful vasectomy (confirmed azoospermia) and do not agree to use condom + spermicide OR have a female partner who does not meet the criteria above (ie, is of childbearing potential and not practicing highly effective contraception throughout the study period), starting with the first dose of study therapy through 120 days after the last dose of study therapy, unless sexually abstinent.
    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
27. Known intolerance to any of the study drugs (or any of the excipients).
28. Subject has had an allogenic tissue/solid organ transplant.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Follow-Up Period and complete protocol-specified off treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the

date will be documented in the source documents. The Subject Disposition CRF page will be completed indicating the primary reason for discontinuation. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing CRF page.

All subjects who discontinue study drug treatment prior to disease progression will continue to undergo tumor assessments every 8 weeks and a bone scan every 24 weeks in the Follow-up Period, until disease progression is documented and confirmed by independent review or a new anticancer therapy is initiated, unless the subject withdraws consent or is lost to follow-up.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

9.4 Treatments

9.4.1 Treatments Administered

Combination lenvatinib plus everolimus arm (Arm A): Lenvatinib 18 mg QD plus everolimus 5 mg QD will be taken orally in each 21-day cycle.

Combination lenvatinib plus pembrolizumab arm (Arm B): Lenvatinib 20 mg QD will be taken orally in each 21-day cycle. Pembrolizumab will be administered at a dose of 200 mg IV over 30 minutes on Day 1 of each 21-day cycle.

Sunitinib arm (Arm C): Sunitinib 50 mg once daily will be administered orally for 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) in each 21-day cycle.

9.4.2 Dose Interruption and Dose Reduction for Combination Lenvatinib plus Everolimus Treatment

Dose reduction and interruptions for subjects who experience lenvatinib everolimus combination therapy-related toxicity will be managed as described in Table 1. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.

The starting dose of lenvatinib is 18 mg/day for subjects enrolled in the combination lenvatinib plus everolimus arm. Lenvatinib dose reductions occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the sponsor. Once the study drug dose has been reduced, it 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.

Refer to the following subsections for management of hypertension (Section 9.4.2.1), proteinuria (Section 9.4.2.2), diarrhea (Section 9.4.2.3), non-infectious pneumonitis (Section 9.4.2.4), infections (Section 9.4.2.5), blood glucose/ lipids (Section 9.4.2.6), hepatotoxicity (Section 9.4.2.7), thromboembolic events (Section 9.4.2.8), posterior

reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS) (Section 9.4.2.9), hypocalcemia (Section 9.4.2.10), and hemorrhage (Section 9.4.2.11), as appropriate, before consulting the dose modification table (Table 1).

Table 1 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 to 14 mg once a day (1-level reduction) 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 to 10 mg once a day (1-level reduction). 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 to 8 mg orally once a day (1-level reduction). 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	Discuss with sponsor
Grade 4[g]: Discontinue Study Treatment		

Note: For grading see CTCAE version 4.03 (Appendix 2). Collect all CTC grades of adverse events, decreasing and increasing grade.
BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events.

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 and/or diarrhea prior to any study treatment interruption or dose reduction.
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 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 1 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.

9.4.2.1 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/sunitinib have BP of ≤150/90 mm Hg 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/sunitinib dose interruptions and reductions.

Regular assessment of BP should be conducted as detailed in the Schedule of Procedures/ Assessments (Table 7 and Table 8). Hypertension will be graded using CTCAE v4.03, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's initial BP measurement is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as one BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes later. 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 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

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

Subjects with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. A diary will be provided to the subject to capture the blood pressure evaluations between study visits.

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

1. Continue study drug 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/sunitinib administration should be interrupted and 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/sunitinib administration should be interrupted and 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/sunitinib administration should be interrupted and restarted at a third dose reduction dose 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 drug.

9.4.2.2 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 are as follows:

<u>Grading of Proteinuria</u>

- Grading according to CTCAE v4.03 will be based on the 24-hour urinary protein result if available.

Management of Proteinuria

- Management of lenvatinib/sunitinib administration will be based on the grade of proteinuria according to the respective treatment arm's Dose Modification Guidelines.
- In the event of nephrotic syndrome, lenvatinib/sunitinib must be discontinued.

Detection and Confirmation

1. Perform urine dipstick testing per the Schedule of Assessments (Table 7 and Table 8)
2. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) or an immediate spot urine protein-to-creatinine ratio (UPCR) test 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/sunitinib dose level
   - When there has been a lenvatinib/sunitinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Monitoring

- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

9.4.2.3 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 respective treatment arm's Dose Modification Guidelines should be followed.

9.4.2.4 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 2016). 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 (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1) may continue study dosing without dose adjustments.

1. 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).
2. 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).
3. If symptoms are life-threatening (CTCAE Grade 4):
   - Study medications should be discontinued.

9.4.2.5 Management of Infections

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

9.4.2.6 Management of Blood Glucose and Lipids

Hyperglycemia, hyperlipidemia and hypertriglyceridemia are recognized class effects of rapamycin derivatives, including everolimus. Glycemic and lipid 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 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.

9.4.2.7 Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the Schedule of Procedures/Assessments and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in the respective treatment arm's Dose Modification Guidelines should be followed.

Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

9.4.2.8 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, 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 respective treatment arm's Dose Modification Guidelines 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.

9.4.2.9 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS)

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, the respective treatment arm's Dose Modification Guidelines should be followed.

9.4.2.10 Management of Hypocalcemia

Serum calcium should be monitored per the Schedule of Procedures/Assessments (Table 7 and Table 8). 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.

9.4.2.11 Management of Hemorrhage

Dose modification guidelines for lenvatinib- (Arm A, Arm B) and sunitinib- (Arm C) related adverse events should be followed for the management of hemorrhage (see Table 1, Table 2, and Table 5). Either resume study drug at a reduced dose or discontinue lenvatinib/sunitinib, depending on the severity and persistence of hemorrhage.

For subjects receiving treatment with sunitinib (Arm C) who experience hemorrhage associated with thrombocytopenia, treatment interruption is recommended; following resolution, treatment may be resumed at the discretion of the investigator.

9.4.3 Dose Interruption and Dose Reduction for Combination Lenvatinib plus Pembrolizumab Treatment

Lenvatinib

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 2. The 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.

The starting dose of lenvatinib is 20 mg/day for subjects enrolled in the combination lenvatinib plus pembrolizumab arm. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the sponsor. Once the study drug dose has been reduced, it 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.

Refer to the following sections for management of hypertension (Section 9.4.2.1), proteinuria (Section 9.4.2.2), diarrhea (Section 9.4.2.3), hepatotoxicity (Section 9.4.2.7), thromboembolic events (Section 9.4.2.8), PRES/RPLS (Section 9.4.2.9), hypocalcemia (Section 9.4.2.10), and hemorrhage (Section 9.4.2.11), as appropriate, before consulting dose modification table (Table 2).

Table 2 Dose Modification Guidelines for Lenvatinib-Related Adverse Events (for the Lenvatinib-Pembrolizumab Combination Arm)

Treatment-Related Toxicity [a,b]	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with sponsor
Grade 4[f]: 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 and/or diarrhea prior to any lenvatinib interruption or dose reduction.

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 (i.e. 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 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 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.

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

Pembrolizumab

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs are reversible and can be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation.

Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitor and Follow-up
General instructions: Corticosteroid taper should be initiated upon AE improving to Grade 0 or 1 and continue to taper over at least 4 weeks. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has improved to Grade 0 or 1 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. **For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.**				
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.	Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) Subjects with Grade ≥2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis
	Grade 4	Permanently discontinue		
AST[a] / ALT[a] elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue		

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitor and Follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for subjects with T1DM . Administer anti-hyperglycemic in subjects with hyperglycemia.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAEv4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitor and Follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician.
For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when the AE improves to Grade ≤2 and is controlled with hormonal replacement therapy or metabolic control is achieved (in the case of T1DM).
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events: GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; T1DM = Type 1 diabetes mellitus.
a: If a subject with liver metastasis has Grade 2 AST or ALT at the start of study treatment, and the AST or ALT value increases by ≥50% relative to Baseline and lasts for ≥1 week, then the subject should permanently discontinue study treatment.

Table 4 shows treatment guidelines for subjects who experience an infusion reaction associated with the administration of pembrolizumab, including premedications.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.**	Subject may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further study treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

CTCAE = Common Terminology Criteria for Adverse Events, version 4.03, IV = intravenous, NCI = National Cancer Institute, NSAID = nonsteroidal antiinflammatory drug.

9.4.4 Dose Interruption and Reduction for Sunitinib

The starting dose of sunitinib is 50 mg/day on a Schedule 4/2 for subjects enrolled in Arm C. See Section 9.4.10.1 for dose recommendations if sunitinib must be co-administered with a strong CYP3A4 inhibitor or inducer.

Dose reduction and interruptions for subjects who experience sunitinib therapy-related toxicity will be managed as described in Table 5. Sunitinib dose reductions occur in succession based on the previous dose level (37.5, 25 mg/day schedule 4/2). Any dose reduction below 25 mg/day must be discussed with the sponsor. Dose modification of sunitinib to a schedule of 2 weeks on treatment followed by 1 week off (Schedule 2/1) is not permitted. Once the study drug dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Refer to the following sections for management of hypertension (Section 9.4.2.1), proteinuria (Section 9.4.2.2), diarrhea (Section 9.4.2.3), hepatotoxicity (Section 9.4.2.7), thromboembolic events (Section 9.4.2.8), PRES/RPLS (Section 9.4.2.9), and hemorrhage (Section 9.4.2.11), as appropriate, before consulting the dose modification table (Table 5).

Table 5 Dose Modification Guidelines for Sunitinib-related Toxicity

Treatment-Related Toxicity [a,b]	During Therapy	Adjusted Dose
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e]		
First occurrence	Interrupt sunitinib until resolved to Grade 0-1, or tolerable Grade 2	37.5 mg daily for 4 weeks followed by 2 weeks off (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt sunitinib until resolved to Grade 0-1, or tolerable Grade 2	25 mg daily for 4 weeks followed by 2 weeks off (1-level reduction)

Table 5 Dose Modification Guidelines for Sunitinib-related Toxicity

Treatment-Related Toxicity [a,b]	During Therapy	Adjusted Dose
Third occurrence (same toxicity or new toxicity)	Interrupt sunitinib	Discuss with sponsor
Grade 4[f]: Discontinue Study Treatment		

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

BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events.

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 and/or diarrhea prior to any study treatment interruption or dose reduction.

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 (i.e. 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 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 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.

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

9.4.5 Identity of Investigational Products

The study drugs under evaluation in this study are 1) lenvatinib in combination with everolimus (Arm A), 2) lenvatinib in combination with pembrolizumab (Arm B), and 3) sunitinib (Arm C). All study drugs will be provided to sites as open-label supplies by the Sponsor.

Lenvatinib will be supplied as 4-mg and 10-mg hard capsules by the sponsor. Lenvatinib is formulated with calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, and talc. The capsule shell contains hypromellose, titanium dioxide (E171), yellow iron oxide (E172), and red iron oxide (E172).

Everolimus will be supplied as 5-mg tablets by the sponsor. Note that everolimus tablets contain lactose.

Pembrolizumab concentrate for solution for infusion will be supplied by the sponsor. Pembrolizumab is provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

Sunitinib will be provided by the sponsor as 12.5-mg and 25-mg hard capsules containing sunitinib malate equivalent to 12.5-mg and 25-mg of sunitinib, respectively.

9.4.5.1 Chemical Name, Structural Formula of Lenvatinib

- Test drug code: E7080
- Generic name: lenvatinib, lenvatinib mesilate, lenvatinib mesylate
- Chemical name: 4-[3-Chloro-4-(*N*'-cyclopropylureido) phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate
- Molecular formula: $C_{21}H_{19}ClN_4O_4 \cdot CH_4O_3S$
- Molecular weight: 522.96
- Structural formula: (see Figure 3)

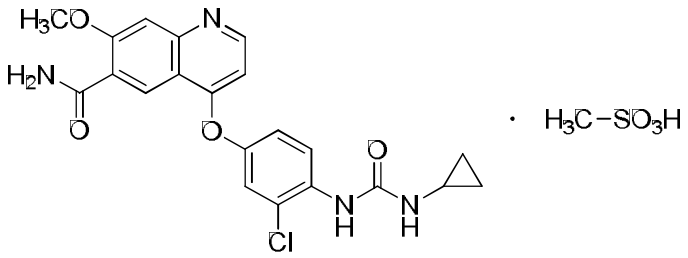

Figure 3 Structural Formula of Lenvatinib Mesilate

9.4.5.2 Chemical Name, Structural Formula of Everolimus

- Generic name: everolimus
- Chemical name: -O-(2-hydroxyethyl)-rapamycin
- Molecular formula: $C_{53}H_{83}NO_{14}$

Refer to the latest AFINITOR® package insert.

9.4.5.3 Information on Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Refer to the latest KEYTRUDA® package insert.

9.4.5.4 Chemical Name, Molecular Formula of Sunitinib

Sunitinib is an oral multi-kinase inhibitor.

- Generic name: sunitinib malate
- Molecular formula: is $C_{22}H_{27}FN_4O_2 \bullet C_4H_6O_5$

Refer to the latest SUTENT® package insert.

9.4.5.5 Labeling for Study Drug

Lenvatinib, everolimus, pembrolizumab, and sunitinib will be provided by Eisai. The everolimus, and sunitinib will be supplied in commercial packaging, which includes the package insert or patient information leaflet. All study drugs will be labeled in accordance with text that is in full compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.5.6 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.6 Method of Assigning Subjects to Treatment Arms

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the Baseline Period, subjects will be randomized to 1 of 3 treatment arms. Each treatment arm will receive 1 of the following treatments: combination lenvatinib plus everolimus, combination lenvatinib plus pembrolizumab, or sunitinib.

Randomization will be performed centrally by an interactive voice and web response system (IxRS) based on the following stratification factors:

- Geographic region: Region 1(Western Europe and North America); Region 2 (rest of the world)
- Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic groups: favorable, intermediate, and poor risk (Appendix 11).

9.4.7 Selection of Doses in the Study

Clinical experience with the combination of lenvatinib 18 mg QD plus everolimus 5 mg QD in Study 205 shows that combination therapy results in significant prolongation of PFS compared with lenvatinib and everolimus as single agents in patients with metastatic RCC. The median PFS of 14.6 months for the combination of lenvatinib and everolimus is clinically relevant and longer than the PFS duration for any other agents approved for

treatment of RCC. The combination of lenvatinib plus everolimus is associated with acceptable and manageable toxicity, with no overlapping or unexpected treatment-emergent adverse events.

The dosage of lenvatinib 20 mg QD plus pembrolizumab 200 mg IV is based on the MTD/RP2D established in Study 111, and the available interim safety and activity results of the Phase 1b/2 portions of Study 111. All but 1 subject with RCC had a best overall response of either partial response or stable disease, and 1 had PD while receiving this treatment. No DLT has been reported thus far in the lenvatinib 20 mg plus pembrolizumab 200 mg cohort. Treatment-emergent AEs reported by ≥30% of subjects in the RCC cohort (in descending order of frequency) were: diarrhea, fatigue, hypothyroidism, nausea, stomatitis, hypertension, cough, dysphonia, proteinuria, arthralgia, decreased appetite, epistaxis, vomiting, constipation, Palmar-plantar erythrodysesthesia syndrome, and weight decreased. Adverse events were managed with supportive care, dose interruptions, and dose reductions.

Sunitinib will be administered at a dosage of 50 mg QD, 4 weeks on, 2 weeks off in accordance with the sunitinib prescribing information in each country/region.

9.4.8 Selection and Timing of Dose for Each Subject

Lenvatinib capsules are to be taken with water orally once a day at approximately the same time each day for 21 days in each cycle from Cycle 1 onward.

If a subject misses a dose of lenvatinib or everolimus, it may be taken within 12 hours following the usual time of the dose. If more than 12 hours have elapsed from the time of the usual daily dose, lenvatinib and/or everolimus should be taken the next day at the usual time. In the event a subject vomits after study drug administration, the subject should not take another dose until the next scheduled dose.

For subjects receiving combination lenvatinib plus everolimus, the 2 drugs should be administered in immediate succession.

For subjects receiving combination lenvatinib plus pembrolizumab, pembrolizumab will be administered at a dose of 200 mg as a 30-minute IV infusion, Q3W (infusion durations of 25 minutes to 40 minutes are acceptable) on Day 1 of each 21-day cycle. The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and its administration. Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. Study treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. On Day 1 (D1) of Cycles 1 and 2, lenvatinib will be administered approximately within 4 hours after completion of pembrolizumab administration.

Sunitinib will be administered orally in accordance with the prescribing information.

9.4.9 Blinding

The study will not be blinded.

9.4.10 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

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 30 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with the study medication may be continued during the study.

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

The following concomitant medications are also allowed:

- Thyroid hormone suppressive therapy
- Adjuvant hormonal therapy for history of definitively treated breast or prostate cancer
- Anticoagulants including low molecular-weight heparin (LMWH), warfarin, anti-Xa agents.
- Antiinflammatory agents
- Bisphosphonates or denosumab
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the subject is enrolled)
- Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases will be permitted without being considered PD.

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

- For minor procedures: stop lenvatinib 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.

9.4.10.1 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 which 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. Please refer to Appendix 1 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.

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Pembrolizumab is a monoclonal antibody; pharmacokinetic interactions with lenvatinib (and vice-versa) are not expected.

Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition or induction is recommended. A dose reduction for sunitinib to a minimum of 37.5 mg daily should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor. A dose increase for sunitinib to a maximum of 87.5 mg daily should be considered if sunitinib must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity. For further information please refer to the prescribing information.

9.4.10.2 Prohibited Concomitant Therapies and Drugs

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Concurrent anticancer therapies such as chemotherapy, TKIs, radiotherapy (with the exception of palliative radiotherapy as specified in Section 9.4.10.1), antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy

- Concurrent other investigational drugs
- For subjects receiving combination treatment with lenvatinib plus everolimus or pembrolizumab, live vaccines are prohibited while participating in the study. Examples of live vaccines include, but are not limited to 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, FluMist®) are live attenuated vaccines, and are not allowed.
- For subjects in the lenvatinib plus pembrolizumab arm (Arm B), systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. Physiologic doses of corticosteroids (up to 10 mg/day of prednisone or equivalent may be used during the study.

  Note: The use of prophylactic corticosteroids to prevent allergic reactions (eg, IV contrast dye or transfusions) is permitted. Inhaled steroids are allowed for management of asthma or seasonal allergies.

For subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor.

If subjects receive additional anticancer therapies, 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 unless they withdraw consent or are lost to follow-up.

For further information on the prohibited concomitant therapies for everolimus, pembrolizumab, and sunitinib please refer to the drug's Prescribing Information.

9.4.11 Treatment Compliance

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

9.4.12 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 Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license (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/study supplies (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs 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.

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, MHRA). As applicable, all unused study drugs and empty and partially empty containers 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

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity

Baseline characteristics will include KPS (Appendix 3), NYHA cardiac disease classification (Appendix 4), and RCC AJCC staging (Appendix 5) at the time of initial diagnosis.

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 7 and Table 8). 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 subject informed consent 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 Eligibility Criteria (Appendix 6). Subjects must also fulfill the medical and physical characteristics identified in the inclusion criteria and not otherwise meet any of the exclusion criteria.

See the Schedule of Assessments (Table 7) for a complete list of baseline assessments.

9.5.1.2 Efficacy Assessments

9.5.1.2.1 TUMOR ASSESSMENTS DURING STUDY TREATMENT

Tumor assessments will be performed using RECIST 1.1 (for all subjects). 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 efficacy assessment. Tumor assessments will be carried out following the guidelines provided by the ICL.

Historical CT or MRI scans performed within 28 days before randomization, but before the signing of informed consent, may be used as screening scans, provided they meet minimum standards as separately defined 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 every 8 weeks from the date of randomization during treatment cycles in the Randomization Phase and as determined by the treating physician in the Extension Phase. The same imaging modality and image-acquisition protocol should be used consistently across all time points. 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 within 6 weeks prior to randomization (historical is acceptable), every 24 weeks after randomization, and within a target of 1 week but no more than 2 weeks following a CR as assessed by the investigator. Lesions identified on bone scans should be followed with cross-sectional imaging.

A brain scan (CT of the brain with contrast or MRI of the brain pre- and post-gadolinium) 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 CR. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at all tumor assessment time points (eg, every 8 weeks).

All subjects will be permitted to continue treatment beyond initial RECIST 1.1-defined progression as long as the investigator believes that the subject is still receiving clinical benefit and is tolerating study drug treatment.

Clinical benefit is defined as:

- Absence of signs and symptoms of PD (including labs)
- No decline in performance status
- Absence of rapid progression of disease
- Absence of progressive tumor(s) at critical sites requiring urgent intervention (eg, spinal cord compression)

The investigator's reason for assessing that a subject is still deriving clinical benefit must be entered into the eCRF. These subjects must continue tumor assessments at the same interval and have copies of all tumor assessments sent to the ICL until further progression and/or loss of clinical benefit, as judged by the investigator. The assessment of clinical benefit should

take into account the potential efficacy benefit versus the safety risk of continuation of treatment. All decisions to continue treatment beyond initial progression determined by the investigator will need to be discussed with the Eisai Medical Monitor and documented in the study records.

To minimize informative censoring, if, at any time during the Randomization Phase, an investigator intends to discontinue a subject from study treatment for disease progression, the ICL must be notified and must confirm (rapid turnaround read within 3-5 working days) that they have assessed PD per RECIST 1.1, before a subject may be discontinued. (However, in situations where the investigator judges that alternative treatments must be instituted immediately for management of urgent medical complications of disease progression, study drug may be discontinued without waiting for independent confirmation of radiographic evidence of disease progression).

In addition, if both independent reviewers assess that a subject has PD during the standard rolling read (timepoints will be read on a rolling basis after they have been reconciled with Eisai's clinical trial database for subject, timepoint, date, anatomy and modality), the investigator will be notified of this finding to assist in their decision as to whether to continue the subject on study treatment.

Subjects who discontinue study treatment without disease progression in the Randomization Phase will continue to undergo tumor assessments every 8 weeks and a bone scan every 24 weeks in the Follow-up Period, until disease progression is documented or another anticancer therapy is initiated. Subjects who have discontinued study treatment without tumor progression in the Extension Phase will have tumor assessments performed as clinically indicated using the investigator's discretion, following the prevailing local standard of care. Copies of tumor assessment scans will no longer be sent to the ICL and independent review will not be carried out during the Extension Phase.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Plasma concentrations of lenvatinib (for subjects in the combination lenvatinib plus everolimus or lenvatinib plus pembrolizumab arms), whole blood concentrations of everolimus (for subjects in the lenvatinib plus everolimus arm only), and serum concentrations of pembrolizumab (for subjects in the lenvatinib plus pembrolizumab arm only) will be measured in all subjects. Lenvatinib and everolimus concentrations will be analyzed using a population PK approach. Data for lenvatinib from this study will be pooled with historical data from other Phase 1 and 2 studies. Data for everolimus from this study will be pooled with data from Study E7080-G000-205. Pembrolizumab concentrations will be compared with historical data. Serum antidrug antibodies (ADA) and neutralizing antibodies (NAb) to pembrolizumab will also be measured for subjects in the lenvatinib plus pembrolizumab arm (Arm B).

Blood samples will be collected as specified in Table 7. Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the laboratory manual.

Samples from all subjects receiving lenvatinib plus everolimus (Arm A) or lenvatinib plus pembrolizumab (Arm B) will be analyzed. Plasma levels of lenvatinib and whole blood levels of everolimus will be quantified by liquid chromatography with tandem mass spectrometry (LC/MS/MS) methodology using previously validated assays. Serum concentrations of pembrolizumab will be measured using validated methods.

9.5.1.3.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Blood and Tissue Biomarkers: Blood samples for the development of exploratory predictive biomarkers will be collected before the first dose of study drug, on Cycle 1 Day 15, and on Day 1 of subsequent cycles (during Treatment / Randomization Phase), and at the off-treatment assessment from all enrolled subjects across the three treatment arms. Biomarker discovery and/or validation may be performed to identify blood or tumor biomarkers that may be useful to predict subject response to study drug, evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Blood samples may undergo global proteomic and/or enzyme-linked immunosorbent assay (ELISA)-based analyses or multiplex bead-based immunoassay, but not limited to, in an effort to identify protein biomarkers. Potential target engagement and pharmacodynamic markers include VEGF, FGF23 and other relevant FGF ligands, Ang-2/Tie-2, and other relevant circulating markers. In addition, biomarkers identified in other clinical studies of study drug may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

The biomarker analysis plan is provided in a separate analysis plan (TSBM-E7080-307-ANA-1P) and the results will be provided in a stand-alone report.

Pharmacokinetic/Pharmacodynamic:

Plasma concentration data for lenvatinib from the combination lenvatinib plus everolimus arm and the combination lenvatinib plus pembrolizumab arm of the study will be used to explore PK/pharmacodynamic relationships for effects of lenvatinib in combination with pembrolizumab or everolimus on PFS, other efficacy-related parameters including ORR and OS, AEs/dose reductions, and blood and tissue biomarkers. Exploratory/graphical analyses will be conducted for PK/pharmacodynamic evaluations and, if possible, will be followed by model-based analyses. Pharmacodynamic data for pembrolizumab (Arm B) will not be measured.

The pharmacodynamic analyses will be detailed in a separate analysis plan (CPMS-E7080-008ADD10 v1.0) and the results will be provided in a stand-alone report.

Pharmacogenetic/Pharmacogenomic (PG) Assessments

Archived, fixed tumor tissue from the most recent surgery or biopsy will be collected (if available) from all enrolled subjects across the three treatment arms for potential assessment of mutations and other genetic alterations or genes and/or proteins that may be important in the development and progression of cancer as well as in response to study drug treatment for potential use in diagnostic development. Genetic alterations in selected molecular targets may be explored based on their potential involvement in renal cell tumor biology (eg, VHL, P I3K-mTOR signaling pathway genes, FGF/FGFR signaling pathway genes, HGF/cMET axis, and/or any known epigenetic modifications). Immune cell profiling and molecular targets and factors involved in immune check-point axis, such as PD1 or PD-L1 levels, markers of Th1/Th2 phenotype, and inflammatory status, may also be explored. Appropriate technology/methodologies will be used based on the amount of tumor tissue available.

A blood plasma sample to isolate circulating cell free nucleic acids and a whole blood sample for immune response profiling will be collected before the first dose of study drug, on Cycle 1 Day 15, and on Day 1 of subsequent cycles (during Treatment/Randomization Phase), and at the off-treatment assessment from all enrolled subjects across the three treatment arms. Cell-free nucleic acid isolated from plasma samples may be used to explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor and to assess the immune response.

A blood sample will be collected for potential PG analysis from all enrolled subjects in treatment arms A and B (in accordance with regional or local laws). Variation in lenvatinib exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data.

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

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual. Refer to Appendix 7 for additional information.

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 2), regular laboratory evaluation for hematology, blood chemistry, and urine values; regular performance of physical examinations, periodic measurement of vital signs, ECGs and MUGA or echocardiogram.

9.5.1.4.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

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

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 AEs must have the AEs leading to screen failure reported on the Screening Disposition CRF. Serious AEs must be collected through 120 days after the subject's last dose of study drug, or for 30 days after the last dose of study drug if the subject initiates new anticancer therapy, whichever is earlier.

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 30 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 2). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

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

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

Classification of Causality

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

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

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

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

9.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

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

- Results in death

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

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

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, blood sample(s) for the measurement of lenvatinib plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

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 6. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 7 and Table 8) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis/urine dipstick testing will be collected in the study.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples (except urine sample for urine dipstick and microscopy) 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.

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 6 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils) 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, CPK[d], Pregnancy test (serum or urine β-hCG)
Urinalysis/Urine Dipstick Testing[e]	glucose, hemoglobin (or blood), ketones, pH, protein[f], specific gravity

β-hCG = beta-human chorionic gonadotropin; CPK = creatine phosphokinase; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

a. INR should only be performed as part of the screening assessment and when clinically indicated.
b. Thyroid function will be assessed every 2 cycles.
c. For subjects with blood glucose >ULN, a fasting (>6h, water only) blood glucose sample will be obtained.
d. CPK isoenzymes (CK-MM and CK-MB) should be evaluated if CPK is greater than 3 × the upper limit of normal.
e. If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.
f. If urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib/sunitinib dose level), then a 24-hour urine collection or an immediate spot urine protein-to-creatinine (UPCR) test should be done to quantify the 24-hour urine protein excretion.

All hematology, clinical chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of Cycle 1, and within 2 business days of receipt of results for all subsequent treatment cycles.

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], heart rate [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 7 and Table 8) 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.

Only 1 BP measurement is needed for subjects with systolic BP <140 mmHg and diastolic BP <90 mmHg. If the subject's initial BP measurement is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

9.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations (including a neurologic examination) will be performed as designated in the Schedule of Procedures/Assessments (Table 7 and Table 8). 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

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 7 and Table 8). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

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

9.5.1.4.7 ECHOCARDIOGRAM OR MULTIPLE-GATED ACQUISITION SCAN

An echocardiogram or MUGA scan (using technetium-based tracer) will be performed to assess left ventricular ejection fraction (LVEF) as designated in the Schedule of Procedures/Assessments (Table 7 and Table 8). MUGA scans or echocardiograms 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.

9.5.1.5 Other Assessments

HRQoL will be assessed at Baseline (prior to first dose of study drug), on Day 1 of each subsequent cycle, at time of withdrawal, 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 FKSI-DRS (Appendix 8), the EORTC QLQ-C30 (Appendix 9), and the EuroQOL EQ-5D-3L (Appendix 1) 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 of 9 multiple-item scales and 6 single items. Multiple-item scales of QLQ-C30 consisted 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 three 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 7 (Prerandomization and Randomization Phase) and Table 8 (Extension Phase) present the schedules of procedures/assessments for the study.

Table 7 Schedule of Procedures/Assessments in Study E7080-G000-307: Prerandomization and Randomization Phases

Phase	**Prerandomization**		**Randomization All Cycles are 21 Days in Duration**								
Period	**Screening[a]**	**Baseline[a]**	**Treatment Period**								**Follow-up Period**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9, etc.**		**98**	**99**
Day	**–28 to –3**	**--3 to –1**	**Cycle 1[b]**			**Cycle 2[c]**		**Cycle 3 – Last[c]**		**Off-Treatment Visit**	
			1	**8**	**15**	**1**	**15**	**1**	**15**		
Procedures/Assessments											
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Randomization[d]			X								
Demographic data	X										
KPS[e]	X	X				X		X		X	
NYHA[e]	X										
RCC AJCC staging (at the time of initial diagnosis of RCC)[e]	X										
Medical/surgical history	X	X									
Phone contact or visit[f]				X							
Vital signs and weight[g]	X	X	X		X	X	X	X	X	X	
Physical Examination[i]	X	X[j]			X	X		X		X	
12-Lead ECG[k]	X		X			X		X		X	
MUGA scan or echocardiogram[l]	X									X	
Hematology and clinical chemistry[m]	X	X			X	X	X	X		X	

Table 7 Schedule of Procedures/Assessments in Study E7080-G000-307: Prerandomization and Randomization Phases

Phase	**Prerandomization**		**Randomization All Cycles are 21 Days in Duration**								
Period	**Screening[a]**	**Baseline[a]**	**Treatment Period**								**Follow-up Period**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9, etc.**		**98**	**99**
Day	**–28 to –3**	**--3 to –1**	**Cycle 1[b]**			**Cycle 2[c]**		**Cycle 3 – Last[c]**		**Off-Treatment Visit**	
			1	**8**	**15**	**1**	**15**	**1**	**15**		
Procedures/Assessments											
Urine dipstick testing[h]	X	X			X	X	X	X	X	X	
Pregnancy test[n]	X	X				X		X		X	X
HRQoL[o]		X				X		X		X	
PK blood sample[p,q]			X		X	X		X			
Pembrolizumab PK blood samples[r]			X			X		X		X	
Biomarker (serum) sample[s]			X		X	X		X		X	
Biomarker (plasma) sample[s]			X		X	X		X		X	
Biomarker (whole blood) sample[s]			X		X	X		X		X	
Tumor assessments (CT/MRI)[t]	X		Performed every 8 weeks (from the date of randomization), or sooner if clinically indicated, until IIR confirmation of disease progression.							X[t,u]	X[t]
Bone Scan[v]	X		Performed every 24 weeks and as clinically indicated.								X[v]
Brain scan[w]	X		X							X[u,w]	X[w]
Archival tumor block or slides[x]			X								
Survival and PFS2[y]											X

Table 7 Schedule of Procedures/Assessments in Study E7080-G000-307: Prerandomization and Randomization Phases

Phase	**Prerandomization**		**Randomization All Cycles are 21 Days in Duration**								
Period	**Screening[a]**	**Baseline[a]**	**Treatment Period**								**Follow-up Period**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9, etc.**		**98**	**99**
Day	**–28 to –3**	**--3 to –1**	**Cycle 1[b]**			**Cycle 2[c]**		**Cycle 3 – Last[c]**		**Off-Treatment Visit**	
			1	**8**	**15**	**1**	**15**	**1**	**15**		
Procedures/Assessments											
Blood sample for PG analysis[z]			X								
Study drug treatment			21 day cycles of lenvatinib daily plus everolimus daily or 21 day cycle of lenvatinib daily plus pembrolizumab IV every 21 days or sunitinib daily for 4 weeks plus 2 weeks off, depending on randomization arm								
Concomitant medications[aa]	Throughout										
AEs/SAEs[bb]	Throughout										

AAE = adverse event; AJCC = American Joint Committee on Cancer; BP = blood pressure; CR = complete response; CT = computed tomography; BW = body weight; C = cycle; D = day; ECG = electrocardiogram; eCRF = electronic case report form; ^{18}F-NaF = ^{18}F-sodium fluoride; HR = heart rate; HRQoL = Health-related Quality of Life; ICF = informed consent form; ICL = imaging core laboratory; IV = intravenous; KPS = Karnofsky performance status; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NAb = neutralizing antibody(ies); NYHA = New York Heart Association; PE = physical examination; PFS2 = progression-free survival after start of next-line therapy; PG = pharmacogenomics; PK = pharmacokinetics; RCC = renal cell carcinoma; RR = respiration rate; SAE = serious AE.

Table 7 Schedule of Procedures/Assessments in Study E7080-G000-307: Prerandomization and Randomization Phases

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. The baseline assessments can be performed within 72 hours or prior to randomization on C1D1. An ICF should be signed by the subject before any screening procedures are performed. Informed consent may be obtained up to 4 weeks prior to C1D1.

b: Efforts should be made to conduct study visits on the day scheduled (± 1 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Procedures/Assessments.

c: Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Procedures/Assessments.

d: Subjects will be randomized on C1D1 (-1 day) after confirmation of eligibility at the Baseline Visit. All procedures and assessments on C1D1 should be performed after randomization.

e: See protocol appendices for KPS assessments, NYHA Cardiac Disease Classification, AJCC Staging.

f: Telephone contact or visit on C1D8 will assess subjects for development of early toxicity. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.

g: Assessments will include vital signs (resting BP [including date and time of measurement for the first 6 treatment cycles], HR, RR, and body temperature) and BW. Only 1 BP measurement is needed for subjects with systolic BP <140 mmHg and diastolic BP <90 mmHg. If the subject's initial BP measurement is elevated (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥ 90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value. Subjects with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 or more frequently as clinically indicated) until their systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. A diary will be provided to the subject to capture the blood pressure evaluations between study visits. See Section 9.4.2.1, *Management of Hypertension*, for further details.

Note: During Cycle 3 and subsequent cycles, subjects may return to the clinic for the Day 15 visit if BP monitoring is required as specified above. The Day 15 visit is mandatory in Cycles 1 and 2.

h: Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles). 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 2 consecutive treatment cycles. For subjects with proteinuria ≥ 2+, see Section 9.4.2.2, *Management of Proteinuria*, for further details.

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.

i: A comprehensive PE (including a neurological examination) will be performed at the Screening or Baseline Visit, on C1D15, on Day 1 of each subsequent cycle, and at the Off-Treatment Visit. A symptom-directed PE will be performed on C1D1 and at any time during the study as clinically indicated. Height will be measured at the Screening Visit only.

j: Required if screening PE is performed >7 days prior to C1D1.

Table 7 Schedule of Procedures/Assessments in Study E7080-G000-307: Prerandomization and Randomization Phases

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

l: MUGA scan or echocardiogram will be performed during the Screening Visit and during or within 1 week following the Off-Treatment Visit, or sooner if clinically indicated. Assessment should use the same methodology (MUGA or echocardiogram).

m: Clinical laboratory tests will be performed at the central laboratory. Every effort will be made to collect samples for analysis at the central laboratory at the same time. Laboratory tests at Baseline may be performed up to 72 hours before randomization. If central laboratory results are not available within the necessary timeframe to allow the subject to be enrolled, local laboratories may be used to perform laboratory test to qualify subjects for entry into the study. Hematology and clinical chemistry 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 patients before starting treatment.
Assessments scheduled may be performed within 72 hours prior to the visit. If ≥ Grade 3 clinically significant hematologic or clinical chemistry toxicities occur, repeat laboratory tests and AE assessments at least every 3-7 days until improvement to < Grade 3. For subjects with blood glucose > ULN, a fasting (> 6h, water only) blood glucose sample will be obtained.

n: A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) at the Screening and Baseline Visits, on Day 1 of each cycle from Cycle 2 onwards, at the Off-Treatment Visit, and every 30 days up to 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first.

o: HRQoL will be assessed at Baseline, on Day 1 of each subsequent cycle, at time of withdrawal 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.

p: Blood samples for PK profiling of lenvatinib (Arms A and B), and everolimus (Arm A), will be drawn 0.5 – 4 and 6 – 10 h postdose on C1D1, predose and 2 – 12 h postdose on C1D15, and predose and 0.5 – 4 and 6 – 10 h postdose on C2D1. Postdose samplings will be omitted if lenvatinib administration is skipped on C1D15 or C2D1. Pharmacokinetic blood samples will be drawn predose only on D1 of Cycles 3, 4, 5, and 6.
NOTE: All lenvatinib predose samples should be taken at least 20 h after the previous dose of lenvatinib, and within 4 h prior to administration of the next dose of lenvatinib (no predose sample is collected on C1D1).

q: If an SAE occurs while the subject is taking lenvatinib, blood sample(s) for PK profiling of lenvatinib should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution, if possible.

r: Blood samples for determination of pembrolizumab, antidrug antibodies (ADA), and neutralizing antibodies (NAb) will be collected prior to pembrolizumab administration on Day 1 of Cycles 1, 2, 3, 5, and during the off-treatment visit after pembrolizumab discontinuation for subjects in Arm B. Additional pembrolizumab PK and ADA samples will be drawn 30 minutes following the end of the pembrolizumab infusion on Day 1 of Cycles 1 and 2 for subjects in Arm B.

s: Collection of blood samples to be used for biomarker studies will be collected from subjects in all treatment arms. Samples will be obtained predose on C1D1, C1D15, Day 1 of all subsequent cycles, and at the Off-Treatment Visit.

t: Screening Period: 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 plus suspected disease should be performed within 28 days prior to randomization. Historical scans performed within the screening period but before signing informed consent may be used if consistent with protocol requirements per imaging core lab.

Treatment Period: 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 plus newly suspected disease should be performed every 8 weeks (starting from date of randomization with a window of ±5 days), or sooner, if clinically indicated. The same methodology (CT or MRI) and scan acquisition techniques that were used for the screening assessments should be followed during the Randomization Phase. Detailed image acquisition guidelines will be provided by the ICL.

All subjects continuing study treatment after initial RECIST 1.1-defined progression must continue tumor assessments at the same interval and have copies of all tumor

Table 7 Schedule of Procedures/Assessments in Study E7080-G000-307: Prerandomization and Randomization Phases

assessments sent to the ICL until further progression and/or loss of clinical benefit as judged by the investigator.

Follow-up Period: Subjects who discontinue treatment without disease progression should continue tumor assessments every 8 weeks until disease progression or beginning another anticancer therapy unless the subject withdraws consent or is lost to follow-up.

u: Tumor assessments at the Off-Treatment Visit (within 1 week of the Off-treatment Visit) are only necessary for subjects who discontinue study drug without disease progression if more than 4 weeks have passed since the previous assessment and if the subject will not continue with follow-up scans. All other subjects will continue tumor assessments as scheduled every 8 weeks from the date of randomization.

v: A bone scan (^{99}m-technetium-based scintigraphy, whole body bone MRI, or ^{18}F-NaF) to assess bone metastases will be performed within 6 weeks prior to randomization (historical scans before signing informed consent are acceptable) and then every 24 weeks (within that 24th week) from randomization or sooner if clinically indicated. In subjects whose body CT/MRI scans indicates 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. If a non-target lesion is being followed by bone scan (not present on CT/MRI), and is not imaged at a follow-up time point because a bone scan is not required at that time point, the time point non-target lesion response will be based upon the other non-target lesions and will not be considered not evaluable (NE).

For subjects who discontinue treatment without disease progression, a bone scan should continue to be performed every 24 weeks in the Follow-up Period until disease progression or beginning another anticancer therapy unless the subject withdraws consent or is lost to follow-up.

w: Screening CT of the brain with contrast or MRI of the brain pre- and post-gadolinium should be performed within 28 days before randomization. During the Randomization Phase, CT/MRI of the brain should be performed if clinically indicated. For subjects with a history of protocol eligible treated brain metastases, a brain scan will be required at all tumor assessment time points (e.g., every 8 weeks). The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability. A brain scan will be performed within a target of 1 week but no more than 2 weeks following achievement of a CR.

For subjects with a history of protocol-eligible, treated brain metastases who discontinue treatment without disease progression, brain scans should continue to be performed every 8 weeks in the Follow-up Period until disease progression or beginning another anticancer therapy, unless the subject withdraws consent or is lost to follow-up.

x: An archival tumor sample from the most recent surgery or biopsy for identification of predictive biomarkers and pathology review will be collected (if available) from all enrolled subjects in all treatment arms at any time during the study, with subject and site approval, and in accordance with regional or local laws.

y: Subjects will be followed for survival and PFS on next-line therapy (PFS2; unless this information is not allowed to be provided due to confidentiality) 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 e-mail.

z: Collection of whole blood to obtain genomic DNA for PG analysis will be obtained on C1D1. Samples will be collected from all subjects receiving lenvatinib (i.e. Arms A and B) only, with subject and site approval, and in accordance with regional or local laws. If sampling is not performed predose, sampling may occur at any subsequent visit in which other blood sampling is scheduled to occur.

aa: Concomitant medications will be recorded for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of survival follow-up.

bb: All AEs will be captured up to 30 days after last dose of study drug. SAEs must be collected through 120 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of the last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to study drug through breastfeeding during study treatment or within 120 days of the last study treatment, or 30 days following the last study treatment if the subject initiates a new anticancer therapy, whichever is earlier, must be reported.

Table 8 Schedule of Visits and Procedures in E7080-G000-307 Extension Phase

Phase	**Extension**			
Period	**Treatment Period**			**Follow-Up Period**
Visit	100-998	101-997	999[p]	1000
	Cycle X (Last Cycle +1) and Beyond[a]		**Off-Treatment Visit**	
Day	1	15		
Assessments				
KPS[b]	X		X	
Vital signs and weight[c]	X	X[c]	X	
Physical Examination[e]	X		X	
12-lead ECG[f]	X		X	
MUGA scan or echocardiogram[g]			X	
Hematology and clinical chemistry[h]	X		X	
Urine dipstick testing[d]	X	X[d]	X	
Pregnancy test[i]	X		X	X
Biomarker (serum) sample[j]			X	
Biomarker (plasma) sample[j]			X	
Biomarker (whole blood) sample[j]			X	
Tumor assessments: CT (MRI)[k]	Tumor assessments will be performed according to the local standard of care.			
Bone Scan	Bone scans will be performed if clinically indicated.			
Brain Scan	Brain scans will be performed if clinically indicated.			
Survival and PFS2[l]				X
Study drug treatment	21-day cycles of lenvatinib daily plus everolimus daily or 21-day cycle of lenvatinib daily plus pembrolizumab IV every 21 days or sunitinib daily for 4 weeks plus 2 weeks off, depending on randomization arm			
Concomitant medications[m]	Throughout		X	
AEs/SAEs[n,o]	Throughout		X	X

Table 8 Schedule of Visits and Procedures in E7080-G000-307 Extension Phase

AEs = adverse events; BP = blood pressure; BW = body weight; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; h = hour(s); HR = heart rate; IV = intravenous; KPS = Karnofsky performance status; med = medication(s); MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NYHA = New York Heart Association; PFS2 = progression-free survival during next-line therapy; RR = respiratory rate; SAEs = serious adverse events; ULN = upper limit of normal; w/in = within.

a. Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Procedures/Assessments.

b. For KPS assessment see protocol appendices.

c. Assessments will include vital signs (resting BP, HR, RR, and body temperature) and BW. Only 1 BP measurement is needed for subjects with systolic BP <140 mmHg and diastolic BP <90 mmHg. If the subject's initial BP measurement is elevated (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (ie, systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value. Subjects with systolic BP ≥160 mm Hg or diastolic BP ≥ 100 mm Hg assessment must have their BP monitored on Day 15 (or more frequently as clinically indicated) until their systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤ 150 mm Hg and diastolic BP has been ≤ 95 mm Hg for 2 consecutive treatment cycles. A diary will be provided to the subject to capture the blood pressure evaluations between study visits. See Section 9.4.2.1, *Management of Hypertension*, for further details.

   Note: During Cycle 3 and subsequent cycles, subjects may return to the clinic for the Day 15 visit if BP monitoring is required as specified above. The Day 15 visit is mandatory in Cycles 1 and 2.

d. Urine dipstick testing for subjects with proteinuria ≥ 2+ should be performed on Day 15 or more frequently as clinically indicated until the results have been 1+ or negative for 2 consecutive treatment cycles. 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 2 consecutive treatment cycles. For subjects with proteinuria ≥ 2+, see Section 9.4.2.2, *Management of Proteinuria*, for further details.

   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.

e. A comprehensive physical exam will be performed on Day 1 of each cycle and at the off-treatment assessment. A physical exam may also be performed on Day 15 or sooner if clinically indicated.

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

g. MUGA or echocardiogram will be performed during or within 1 week following the off-treatment assessment, or sooner if clinically indicated. MUGA scans or echocardiogram will be performed in accordance with the institution's standard practice. Assessment should use the same methodology (MUGA or echocardiogram).

h. Hematology and clinical chemistry results (central or local) must be reviewed within 2 business days of receipt of results for all subsequent cycles.

Table 8 Schedule of Visits and Procedures in E7080-G000-307 Extension Phase

Assessments scheduled may be performed within 72 hours prior to the visit. If local laboratory results are used, they should be entered on an unscheduled eCRF for that visit. If ≥ Grade 3 clinically significant hematologic or clinical chemistry toxicities occur, repeat laboratory tests and AE assessments at least every 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.

i. A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) on Day 1 of each cycle from Cycle 2 onwards, at the Off-Treatment Visit and every 30 days up to 120 days post last dose of the study medication or the start of a new anticancer therapy, whichever comes first.

j. Collection of blood samples to be used for biomarker studies will be collected from subjects in all treatment arms at the Off-Treatment visit.

k. Extension Phase: Tumor Assessments should be performed according to the local standard of care, but not less frequently than every 12 weeks. 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 during the Extension Phase. During the extension phase scans will no longer be sent to the imaging core lab.

l. Subjects will be followed for survival and PFS on next-line therapy (PFS2; unless this information is not allowed to be provided due to confidentiality) every 12 weeks (±1 week) after the Off-Treatment Visit unless they withdraw consent or are lost to follow-up. If a clinic visit is not feasible, follow up information may be obtained via telephone or e-mail.

m. Concomitant medications will be recorded for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of survival follow up.

n. All AEs will be captured up to 30 days after last dose of study drug. SAEs must be collected through 120 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of the last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to study drug through breastfeeding during study treatment or within 120 days of the last study treatment, or 30 days following the last study treatment if the subject initiates a new anticancer therapy, whichever is earlier, must be reported.

o. If an SAE occurs while the subject is taking lenvatinib, blood sample(s) for PK profiling of lenvatinib should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution, if possible.

p. The off-treatment assessments should occur within 30 days of the final dose of study treatment.

9.5.2.1 Description of Procedures/Assessments Schedule

Refer to Table 7 and Table 8 for description and timing of each procedure and assessment in the Prerandomization and Randomization Phase and the Extension Phase, respectively

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.

SAEs regardless of causality assessment must be collected through the last visit and for 120 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier.

Regardless of treatment arm, 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 120 days of the last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to study drug through breastfeeding during study treatment or within 120 days of the last study treatment, or 30 days following the last study treatment if the subject initiates a new anticancer therapy, whichever is earlier, must be reported.

Regardless of treatment arm, 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 the time that 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 the time that the investigator becomes aware of the outcome.

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

9.5.4.3 Reporting of Events Associated with Special Situations

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

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

Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol

Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

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

Note: Overdose for pembrolizumab is defined as a dose greater than 5 times the 200 mg dose.

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

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

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

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 suspected unexpected serious adverse reactions (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 7 and Table 8).

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. Study disposition information will be collected on the Subject Disposition CRF.

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 end of the Randomization Phase after database lock and randomization codes have been released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP), which will be finalized before the database lock.

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint is PFS by independent review defined as the time from the date of randomization to the date of the first documentation of disease progression per RECIST 1.1 or death (whichever occurs first). PFS censoring rules will follow the FDA guidance of 2007; specifics of this will be detailed in the Statistical Analysis Plan.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints are as follows:

- Objective response rate (ORR) is defined as the proportion of subjects who have best overall response of CR or PR as determined by IIR using RECIST 1.1.
- Overall survival (OS) is defined as the time from the date of randomization to the date of death from any cause. Subjects who are lost to follow-up and those who are alive at the date of data cut-off will be censored at the date the subject was last known alive, or date of data cut-off, whichever occurs first.
- Safety will be assessed summarizing the incidence of treatment-emergent adverse events (TEAEs) and SAEs together with all other safety parameters.
- Proportion of subjects who discontinued treatment due to toxicity is defined as the proportion of subjects who discontinue study treatment due to treatment-emergent adverse events (TEAEs).
- Time to treatment failure due to toxicity is defined as the time from the date of first dose to the date that a subject discontinues study treatment due to TEAEs.

- 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.
- PFS on next-line of therapy (PFS2) is defined as the time from randomization to disease progression on next-line of treatment, or death from any cause, (whichever occurs first).
- Progression-free survival (PFS) by investigator assessment is defined as the time from the date of randomization to the date of first documentation of disease progression based on the investigator assessment per RECIST v.1.1 or death (whichever occurs first).
- Model-predicted clearance and AUC for lenvatinib in Arms A and B.
- Model-predicted clearance and AUC for everolimus in Arm A.

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints are as follows:

- Duration of response (DOR) is defined as the time from the date a response was first documented until the date of the first documentation of disease progression or date of death from any case.
- Disease control rate is the proportion of subjects who have best overall response of CR or PR or SD. Stable disease must be achieved at ≥ 7 weeks after randomization to be considered best overall response.
- Clinical benefit rate is the proportion of subjects who have best overall response of CR or PR or durable SD (duration of SD ≥ 23 weeks after randomization).
- Blood and tumor biomarkers will be assessed for identifying potential correlation with clinical outcomes-related endpoints.

9.7.1.2 Definitions of Analysis Sets

The Full Analysis Set (Intent-to-Treat Analysis [ITT] Population) is the group of all randomized subjects regardless of the treatment actually received. This is the primary analysis population used for all efficacy analyses which will be based on the intent-to-treat principle.

The Per Protocol Analysis Set is the group of those subjects who received at least 1 dose of study drug, had no major protocol deviations and had both baseline and at least 1 postbaseline tumor assessments. Subjects for whom death occurred prior to the first postbaseline tumor assessment will also be included. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug. This is the analyses population used for all safety analyses which will be based on as-treated principle.

Population Pharmacokinetic (PK) Analysis Set: All the subjects who have received at least 1 dose of study treatment with documented dosing history in the lenvatinib plus everolimus arm (Arm A) or the lenvatinib plus pembrolizumab arm (Arm B), and have measurable plasma levels of lenvatinib, or whole blood levels everolimus.

Pembrolizumab Pharmacokinetic (PK) Analysis Set: All subjects who have received at least 1 dose of study treatment with documented dosing history in the lenvatinib plus pembrolizumab arm (Arm B) and have measurable serum concentrations of pembrolizumab.

The Pharmacodynamic Analysis Set is the group of subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data to derive at least 1 pharmacodynamic measurement and with documented dosing history.

The QOL Analysis Set will consist of all subjects who have any QOL data.

9.7.1.3 Subject Disposition

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 for the full analysis set will be summarized for each treatment arm and for all treatment arms combined using descriptive statistics. Continuous demographic and baseline variables include age, body weight, and height; categorical variables include sex, age group, race, region, KPS, NYHA cardiac disease classification, MSKCC prognostic group, and AJCC staging at the time of diagnosis.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. The number (percentage) of subjects who took prior and concomitant medications will be summarized on full analysis set by treatment arm, Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term. Prior medications will be defined as medications that started before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Comparisons of PFS between lenvatinib + everolimus (Arm A) versus sunitinib (Arm C), and lenvatinib + pembrolizumab (Arm B) versus sunitinib (Arm C) will be performed. PFS will be evaluated using Kaplan-Meier (K-M) estimates and the statistical significance of the difference in PFS for the 2 primary comparisons will be tested by stratified logrank test. Geographic region and MSKCC prognostic groups will be used as stratification factors for randomization. The hazard ratio (lenvatinib + everolimus relative to sunitinib and lenvatinib + pembrolizumab relative to sunitinib) and the corresponding 95% confidence intervals (CIs) will be estimated using the Cox regression model with Efron's method for handling tied results, stratified by the same stratification factors.

An interim and a final analysis of PFS are planned to be performed (Section 9.7.3). Lan-DeMets spending function with O'Brien-Fleming boundary will be used to control alpha levels between the interim and final analysis of PFS. The interim analysis of PFS will be performed when it is approximately 4 months after the last subject is randomized and an approximately 80% information fraction of PFS events (as determined by the IIR) in Arm B and Arm C. The final analysis of PFS will be performed when approximately 388 PFS events, as determined by the IIR, are observed between each comparison. A graphical approach (Section 9.7.4) will be used to control the family wise error rate (FWER) at the two-sided 0.0499 for multiple comparisons, including both PFS comparisons of Arm B vs Arm C and Arm A vs Arm C. For each comparison, a statistical significance can be claimed based on either interim or final analysis of PFS at specified alpha levels.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

Overall Survival (OS) will be compared between lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and lenvatinib + pembrolizumab (Arm B) vs. sunitinib alone (Arm C) using the stratified logrank test with geographic region (Western Europe and North America vs. Other) and MSKCC prognostic groups (favorable, intermediate and poor risk) as strata. The hazard ratio and its 95% CI comparing lenvatinib + everolimus (Arm A) vs. sunitinib alone (Arm C) and lenvatinib + pembrolizumab (Arm B) vs. sunitinib alone (Arm C) will be estimated by a stratified Cox proportional hazards model with Efron's method for handling tied results, stratified by geographic region and MSKCC prognostic groups. Median OS with 2-sided 95% CIs will be calculated using K-M product-limit estimates for each treatment arm and K-M estimates of OS will be plotted over time.

Three interim and final OS analyses are planned to be performed (Section 9.7.3). Lan-DeMets spending function with Pocock boundary will be used to control alpha levels among the interim and final analysis of OS. The first two OS interim analyses will be performed at the time of PFS interim and final analysis, corresponding to approximately 45% and 60% of information fractions of OS events. The third OS interim analysis will be performed at approximately 80% information fraction of OS events. The final analysis of OS will be performed when 304 OS events are observed for each comparison. Objective Response Rate (ORR) will be calculated with exact 95% confidence intervals using the method of Clopper

and Pearson. The difference between treatment arms will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by geographic region and MSKCC prognostic groups. The p-value for hypothesis testing of ORR will be based on the ORR data at the time of the PFS interim analysis. The ORR data available at the subsequent analysis time points will be provided for supportive purposes.

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 EMA 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.

PFS2 will be calculated using the Kaplan-Meier (KM) product-limit estimates for each treatment group and presented with two-sided 95% CIs. The KM estimate of PFS2 will also be plotted over time for each treatment group.

PFS by investigator assessment per RECIST v1.1 will be analyzed similarly as for the primary endpoint of PFS by IIR per RECIST v1.1.

The strategy to address multiplicity and control of the overall FWER for the primary and key secondary efficacy endpoints is described in 9.7.4.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Disease Control Rate and CBR will be calculated with exact 95% confidence intervals using the method of Clopper and Pearson. The differences and odds ratios of the above rates between treatment arms and corresponding two-sided 95% CIs will be calculated respectively. Median duration of response among responders for each treatment arm will be presented along with its corresponding 2-sided 95% CIs.

The difference in PFS between lenvatinib in combination with everolimus versus lenvatinib in combination with pembrolizumab will be analyzed using the methods used for analysis of the primary endpoint.

No multiplicity adjustment will be made for testing exploratory endpoints.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Plasma concentrations of lenvatinib and whole blood concentrations of everolimus versus time data will be analyzed using a population PK approach to estimate population PK parameters for each respective drug, while pembrolizumab concentrations will be compared with historical data. For lenvatinib, data from this study will be pooled with historical data

from other Phase 1 and 2 studies. For everolimus, data from this study will be pooled with data from Study E7080-G000-205.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Soluble, tissue, genetic and/or imaging biomarkers (baseline and/or post-treatment) may be summarized using descriptive statistics and correlated with clinical outcomes-related endpoints for safety and/or efficacy (including best overall response, PFS and OS) as appropriate. Details may be included in a separate analysis plan.

9.7.1.7.3 PHARMACOKINETIC-PHARMACODYNAMIC ANALYSES

The effect of lenvatinib in combination with everolimus or pembrolizumab on soluble, tissue, genetic and/or imaging biomarkers will be summarized using descriptive statistics using the PK/pharmacodynamic analysis set. PK/pharmacodynamic relationships (ie, exposure-efficacy, and exposure-safety and exposure-biomarker relationships) will be modeled, if possible, using a mechanistic approach for effects of study treatment. Efficacy endpoints will include the primary endpoint of PFS and other efficacy-related metrics including but not limited to ORR (based on RECIST 1.1) and OS. Safety endpoints will be most frequent AEs of special interest and dose reductions. Exploratory/graphical analyses will be conducted for PK/pharmacodynamic evaluations, and, if possible, will be followed by model-based analyses.

The PK and PK/PD analyses will be detailed in a separate analysis plan that will be provided at a later date and the result will be provided in a standalone report.

9.7.1.8 Safety Analyses

Safety analyses will be based on the Safety Analysis Set. All safety analyses will be summarized by treatment arm. Adverse events and serious adverse events, laboratory test results, vital signs, and echocardiogram results (including LVEF) will be summarized. Safety data will be summarized using descriptive statistics. Categorical variables will be summarized by number and percentage. Continuous variables will be summarized using n (number of subjects with available data), mean, standard deviation, median, Q1, Q3, and range (minimum and maximum) unless otherwise specified.

9.7.1.8.1 EXTENT OF EXPOSURE

The number of cycles/days on treatment, quantity of study drugs 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.

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

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include TEAEs that were considered by the Investigator to be possibly or probably related to study drug or TEAEs with a missing causality. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (by highest CTCAE grade).

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

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 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, resting HR, respiratory rate, temperature, and weight) and changes from baseline will be presented by visit and treatment arm. Blood pressure will also be summarized using a shift table by categories defined based on CTCAE Grades. Subjects will be included in the summary if they had both a Baseline value and at least 1 postbaseline value for blood pressure.

9.7.1.8.5 ELECTROCARDIOGRAMS

Change from baseline to worst postbaseline result in ECG findings (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) will be summarized by treatment arm using a shift tables. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit by treatment arm.

9.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive statistics for LVEF assessed on echocardiogram or MUGA scans and changes from baseline will be presented by treatment arm. Percent reduction from baseline will also be summarized.

9.7.2 Determination of Sample Size

The sample size is estimated based on the primary endpoint of PFS. Approximately 1050 subjects will be randomized in a 1:1:1 ratio into 1 of 3 treatment arms: lenvatinib + everolimus, lenvatinib + pembrolizumab, or sunitinib alone. The randomization scheme will be stratified by geographic region (Western Europe + North America vs. Other) and MSKCC prognostic groups (favorable, intermediate and poor risk).

The same treatment effect is assumed for the primary comparisons of lenvatinib + everolimus (Arm A) and lenvatinib + pembrolizumab (Arm B) each compared to sunitinib alone (Arm C). Assuming the median PFS of sunitinib to be 12.3 months and a targeted HR of 0.714 for the primary comparisons, this corresponds to a 40% improvement (4.9 months) in median PFS from 12.3 months to 17.2 months for Arm A versus Arm C and for Arm B versus Arm C. A yearly loss of PFS event rate of 22% is assumed in the sample size calculation.

Since the study is testing more than one comparison for the primary and secondary endpoints, the graphical approach (Section 9.7.4) will be used for testing multiple hypotheses. For the two PFS comparisons (one for each test arm), the sponsor chooses to split the total alpha of 0.0499 (2-sided), as initial allocations, into $\alpha = 0.045$ for the comparison between Arm B and Arm C, and $\alpha = 0.0049$ for the comparison between Arm A and Arm C.

The study is designed to achieve 90% power at $\alpha = 0.045$ to detect a statistically significant difference in PFS in the comparison between Arm B and Arm C. Therefore, a total of 388 PFS events are required between Arms B and C in the final PFS analysis. Since the same number of PFS events are expected to be observed in Arms A and C, a total of 388 PFS

events is expected in the final PFS analysis for the comparison between Arms A and C. The power to detect a statistically significant difference in PFS between Arm A and Arm C is approximately 70% at the initial assigned $\alpha = 0.0049$, and will be at least 90% when the hypothesis tests of PFS and OS in the comparison of Arm B and Arm C are statistically significant, and vice versa. In the power calculation for PFS analysis, it is assumed that one interim analysis of PFS is to be performed at the 80% information fraction and a Lan-DeMets spending function with O'Brien-Fleming boundary is used between the interim and final analysis of PFS.

Assuming an average enrollment rate of 31 subjects per month, the interim and final analysis of PFS will occur approximately 38 and 45 months (34-month enrollment period) after the first subject is randomized. A total of 582 PFS events are expected in 3 arms by the time of planned final PFS analysis.

For the key secondary endpoint of OS, a total of 304 deaths for each comparison (456 death events among the 3 arms) are expected in the final OS analysis. For OS testing, when the corresponding PFS testing is statistically significant at the initial assigned alpha, the study will provide 80% power to detect a statistically significant difference at an α level of 0.045 for the comparison between Arms B and C, and 50% power at an α level of 0.0049 for the comparison between Arm A and C. By using the graphical approach, the power for the OS comparison between Arms A and C will increase to at least 80% when the OS testing between Arms B and C is significant and both PFS testings are significant, and vice versa. The assumptions that are used for the OS power calculations are: 1) the hazard ratio is 0.70 (median OS is 54.1 months in Arm A or Arm B and 37.9 months in Arm C), 2) interim analyses are performed at approximately 45%, 60%, and 80% information fraction of death events, 3) a Lan-DeMets spending function with Pocock boundary is used, and 4) the yearly rate for loss to follow-up is 3%. With the planned sample size and the assumptions for enrollment, the final analysis of OS is expected to occur approximately 69 months after the first subject is randomly assigned to treatment.

For the key secondary endpoint of ORR, assuming an ORR of 32% in Arm C and 48% in Arm A or Arm B, the study will provide at least 95% power to detect a difference when testing of PFS and OS are positive for each comparison of Arm B vs Arm C and Arm A vs Arm C.

9.7.3 Interim Analysis

The interim efficacy analyses will be conducted by an independent statistical group that has no other responsibilities for the study. The safety monitoring will be conducted by the independent DMC and only the DMC will have access to data with treatment information. The frequency of the safety reviews will be defined in the DMC charter. Minutes from the open meetings of the DMC will be provided if requested by regulatory agencies and the DMC closed minutes will be provided after the end of the study. The recommendation whether to stop the trial for safety reasons will be reached by the DMC based on its review of safety data with treatment information. The function and membership of the DMC will be described in the DMC charter.

Interim analyses of PFS, OS, and ORR are planned in this study. The timing of each analysis are summarized in Table 9. Type I error control for the efficacy analyses as well as efficacy boundaries are described in 9.7.4.

Table 9 Summary of Interim and Final Efficacy Analyses

No.	Analysis	Endpoint(s)	Timing	Estimated Time after First Subject Randomized
1	Interim analysis of ORR and DOR (the first 88 subjects from Arm B)	ORR DOR	Median follow-up of 12 months and a minimum DOR follow-up of 6 months	~28 months
2	Interim analysis of PFS, Interim analysis of OS	PFS OS ORR*	Trigger: approximately 4 months after the last subject randomized and approximately 310 (80% IF) PFS events observed in Arms B and C (estimated to have ~140 (45% IF) deaths observed for each comparison)	~38 months
3	Final analysis of PFS,Interim analysis of OS	PFS OS	Trigger: ~ 388 PFS events observed for each comparison (estimated to have 182 (60% IF) deaths observed for each comaprison)	~45 months
4	Interim analysis of OS	OS	Trigger: ~243 (80% IF) deaths observed for each comparison	~57 months
5	Final analysis of OS	OS	Trigger: ~304 deaths observed for each comparison	~69 months

DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; IF=information fraction.
*: The p-value for hypothesis testing of ORR will be based on the ORR data at the analysis No 2.

An interim analysis of ORR for the first 88 subjects from the lenvatinib + pembrolizumab arm (Arm B) of this study will be performed. No comparative analysis will be conducted for the interim analysis of ORR; however, an α of 0.0001 will be allocated and deducted from the analyses of PFS. Details outlining how the integrity of study conduct will be maintained are described in a separate operational plan. This interim analysis of ORR will occur after the first 88 subjects treated in Arm B (lenvatinib + pembrolizumab) have completed a median follow-up of 12 months and a minimum DOR follow-up of 6 months.

In Table 9, another operational plan will be prepared for the analyses specified at Analysis No. 2-5 and this plan will include a procedure to conduct an independent statistical review for monitoring the number of events specified as triggers.

9.7.4 Multiplicity

To adjust for multiplicity and control the overall FWER, the graphical approach of Maurer and Bretz (Maurer et al., 2013) will be used in the primary endpoint of PFS and the key

secondary efficacy endpoints (OS and ORR). No multiplicity adjustment will be made for other secondary endpoint analyses. An α of 0.0001 will be subtracted from the total α of 0.05 to account for the interim analysis of ORR from Arm B. Figure 4 shows the initial α-allocation (the remaining α of 0.0499) for each hypothesis and the graphical approach for multiple analyses of PFS, OS, and ORR.

If the null hypothesis of PFS is rejected at the initial allocated alpha level 0.045 for H_1 (or 0.0049 for H_2), this alpha of 0.045 (or 0.0049) will be reallocated to the tests with the corresponding weights as shown in Figure 4. The initial weights for reallocation from each hypothesis to the others are represented by the numbers next to the arrows (eg, if H_1 and H_3 are positive, 90% alpha will be reallocated to H_2, and 10% to H_5). An alpha level 0.045 is assigned to H_1 to increase the successful rate of H_1 test so that this alpha can be re-allocated to other hypothesis tests. When alpha is re-allocated as planned for all hypotheses, the PFS tests H_1 and H_2 will both have 90% power, OS tests H_3 and H_4 will both have 80% power, and the ORR tests H_5 and H_6 will both have more than 95% power.

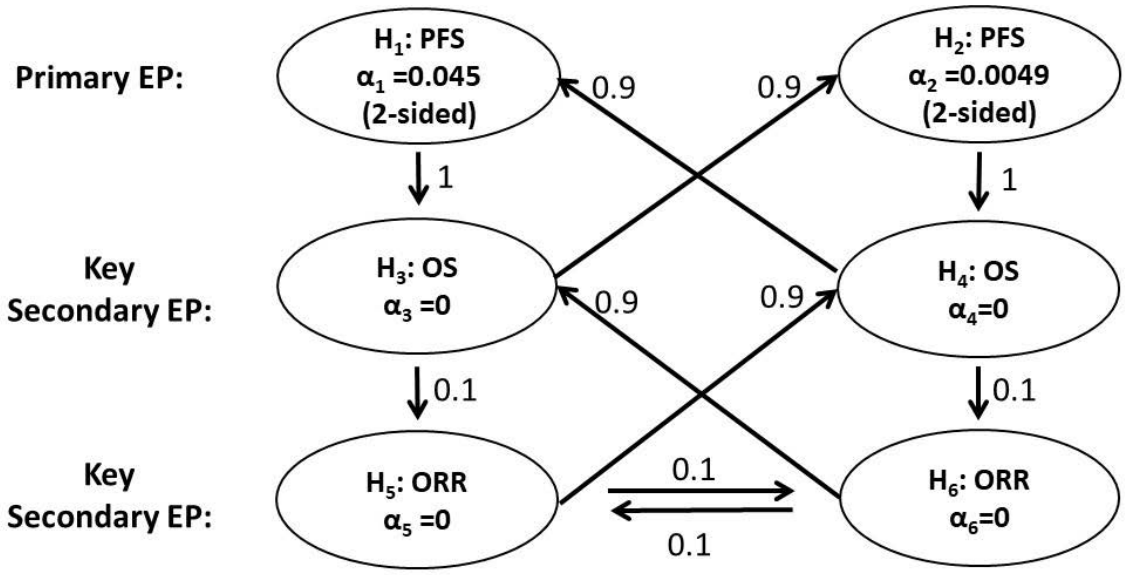

Figure 4 Graphical Approach to Control Familywise Error Rate for Testing Primary and Key Secondary Endpoints

EP = endpoint; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
Hypothesis (H_1): The PFS of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_2): The PFS of lenvatinib + everolimus arm is superior to that of sunitinib arm.
Hypothesis (H_3): The OS of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_4): The OS of lenvatinib + everolimus is superior to that of sunitinib arm.
Hypothesis (H_5): The ORR of lenvatinib + pembrolizumab arm is superior to that of sunitinib arm.
Hypothesis (H_6): The ORR of lenvatinib + everolimus is superior to that of sunitinib arm.

The nominal α level for each PFS comparison at the interim and final analyses will be determined by a Lan-DeMets spending function with an O'Brien-Fleming boundary as illustrated in Table 10. The nominal α level for each OS comparison at the interim and final analyses will be determined by a Lan-DeMets spending function with Pocock boundary as illustrated in Table 11. The actual boundaries will be calculated using the observed number of events at the interim and final analyses and α passed from previous tests.

The study will continue unless the sponsor decides to discontinue survival follow-up following completion of the PFS analysis when appropriate, eg, when only a minimal number of subjects remain in follow up.

Table 10 Efficacy Boundaries and Properties for PFS H_1 and PFS H_2 (LDOF spending function) Based on Initial Assigned Alpha

Analysis (2 arms)	Value	H_1 (α=0.045)	H_2 (α=0.0049) [d]
IA: 80%[a] N: 700 Events: 310 Month: 38	*P* (2-sided)[b]	0.0216	0.0014
	HR at boundary[c]	0.7705	0.6964
	Power	75%	42%
Final: 100% N: 700 Events: 388 Month: 45	*P* (2-sided)[b]	0.0386	0.0046
	HR at boundary[c]	0.8105	0.7491
	Power	90%	69%

HR = hazard ratio, IA = interim analysis, N = number of subjects.
a: Information fraction, percentage of expected number of events at final analysis.
b: P-value (2-sided) is the nominal α for testing.
c: HR at boundary is the approximate HR required to reach an efficacy boundary.
d: The power of H_2 test will be at least 90% if H_1 and H_3 testings are significant.

Table 11 Efficacy Boundaries and Properties for OS H_3 and OS H_4 (LD-Pocock Spending function) when PFS Tests Are Significant

Analysis (2 arms)	Value	H_3 (α=0.045)	H_4 (α=0.0049) [d]
IA: 45%[a] N: 700 Events: 137 Month: 38	*P* (2-sided)[b]	0.0258	0.0028
	HR at boundary[c]	0.683	0.600
	Power	44%	20%
IA: 60%[a] N: 700 Events: 182 Month: 45	*P* (2-sided)[b]	0.0152	0.0014
	HR at boundary[c]	0.698	0.622
	Power	55%	27%
IA: 80%[a] N: 700 Events: 243 Month: 57	*P* (2-sided)[b]	0.0158	0.0014
	HR at boundary[c]	0.734	0.663
	Power	69%	41%

Final: N: 700 Events: 304 Month: 69	*P* (2-sided)[b]	0.0158	0.0014
	HR at boundary[c]	0.758	0.692
	Power	80%	51%

HR = hazard ratio, IA = interim analysis, N = number of subjects.
a: Information fraction, percentage of expected number of events at final analysis.
b: P-value (2-sided) is the nominal α for testing.
c: HR at boundary is the approximate HR required to reach an efficacy boundary.
d: The power of H_4 test will be at least 80% if H_1, H_3 and H_2 are significant.

9.7.5 Other Statistical/Analytical Issues

Not applicable.

9.7.6 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.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor (or appropriate study team member) 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 correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

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

11.5 Identification of Source Data

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

- Study drug compliance (eg, the reason for any change of dosage)
- Indication for prior/concomitant medication (drug/therapy)
- Discontinuation information (eg, in the case of lost to follow-up due to the subject choice)
- Sampling date and time for the drug concentration
- Sampling date for the clinical laboratory tests

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

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

11.12 Subject Insurance and Indemnity

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

12 APPENDICES

Appendix 1 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 2 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 the Cancer Therapy Evaluation Program, NCI. CTCAE v4.03	

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

Appendix 3 Karnofsky Performance Status Scale

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 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

Oxford Textbook of Palliative Medicine, Oxford University Press 1993;109.

Appendix 4 New York Heart Association (NYHA) 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; 1994:253-6.

Appendix 5 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 node (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: pp 479-89.

Appendix 6 Response Evaluation Criteria in Solid Tumors (RECIST)

Tumor response assessments in this clinical trial will use Response Evaluation Criteria in Solid Tumors (mRECIST) 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. As required by RECIST 1.1, the protocol states that the minimum duration of SD is 7 weeks.

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

Appendix 7 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic, pharmacogenomic (PG), 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.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the pharmacodynamic, PG, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for pharmacodynamic, PG, 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. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

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

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis 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.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

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. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." 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, PG, 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, PG, 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 8 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 past 7 days.**

		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

Appendix 9 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 10 Health-Related Quality of Life Questionnaire EQ-5D-3L

Health Questionnaire

English version for the UK

(Validated for Ireland)

By placing a tick 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 ❑

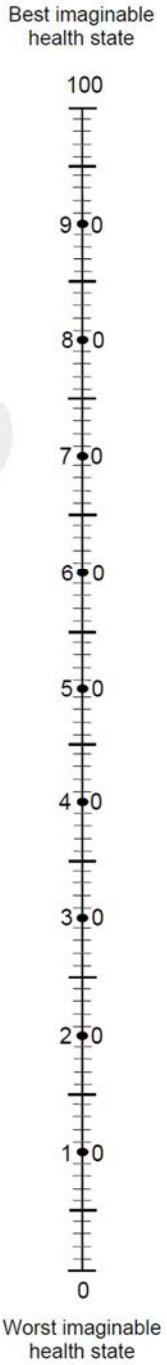
Anxiety / Depression

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



3

Appendix 11 MSKCC Risk Model Criteria

Determination of Prognostic Score in First Line Setting

Parameter	Criteria Value	Subject Value	If subject value meets criteria value, enter 1
KPS, %	< 80		
Time from initial RCC diagnosis to treatment with systemic therapy, in months	< 12		
Hemoglobin	< LLN		
Lactate Dehydrogenase (LDH)	> 1.5 x ULN		
*Corrected Calcium, mg/dL	> 10.0		
			Sum total of above= MSKCC Prognostic Score:

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

KPS = Karnofsky Performance Status; LLN = lower limit of normal; MSKCC = Memorial Sloan-Kettering Cancer Center; RCC = renal cell carcinoma; ULN = upper limit of normal.

* 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.

Risk Group Based on MSKCC Prognostic Score

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

MSKCC = Memorial Sloan-Kettering Cancer Center.

Appendix 12 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, et al. Nephron. 1976;16(1):31-41.

For serum creatinine measured in μmol/L:

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

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

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E7080-G000-307
Study Protocol Title:	A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma.
Investigational Product Name:	lenvatinib (E7080), everolimus, pembrolizumab, and sunitinib
IND Number:	124564
EudraCT Number:	2016-000916-14

SIGNATURES

Authors:

PPD

11-Aug-2020
Date

Oncology Business Group, Eisai Inc.

PPD

13-Aug-2020
Date

Oncology Business Group, Eisai Ltd.

PPD

12-Aug-2020
Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-G000-307
Study Protocol Title:	A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma.
Investigational Product Name:	lenvatinib (E7080), everolimus, pembrolizumab, and sunitinib
IND Number:	124564
EudraCT Number:	2016-000916-14

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

Medical Institution

Investigator	Signature	Date

As regionally required

Head Medicine Development Center	Signature	Date