1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-A001-111
Study Protocol Title:	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	Lenvatinib (E7080) and Pembrolizumab (MK-3475/KEYTRUDA®)
Indication:	Solid tumors
Phase:	Phase 1b/2
Approval Date(s):	22 Apr 2015 — Original Protocol 14 Jan 2016 — Protocol Amendment 1 30 Mar 2016 — Protocol Amendment 2 26 Oct 2016 — Protocol Amendment 3 23 May 2017 — Protocol Amendment 4 22 Dec 2017 — Protocol Amendment 5 31 Jul 2018 — Protocol Amendment 6 19 Apr 2019 — Protocol Amendment 7 24 Aug 2020 — Protocol Amendment 8 30 July 2021 — Protocol Amendment 9
IND Number:	72010
EudraCT Number:	2017-000300-26
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice

	(GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

REVISION HISTORY

Amendment 09

Date: 30 July 2021

Change	Rationale	Affected Protocol Sections
Revised and added text to clarify when treatment in the study would be discontinued, subject choice, completion of 35 treatments (approximately 2 years) with pembrolizumab, and lost to follow up. Added text to specify that the subjects who discontinued pembrolizumab for any reason and were still receiving lenvatinib study drug, will be transitioned to commercial lenvatinib if local country regulations permit.	To clarify when treatment in the study would be discontinued. To define when subjects could be transitioned to treatment with commercial lenvatinib.	• Synopsis, Study Design • Section 9.1 • Synopsis, Study Design • Section 9.1
Revised the frequency of tumor assessments in the Phase Ib and Phase 2 Extension Phase per local standard of care but not less frequent than every 6 months. Tumor assessments will not be collected during the Follow-Up period of the Extension Phase.	To align with the standard of care for treatment of patients in the disease population and to clarify that the tumor assessment results will not be collected in the Follow-Up Period of the Extension Phase after the primary endpoint analysis in the study has been completed.	• Synopsis, Study Design • Section 9.1 • Section 9.5.1.3 • Section 9.5.2, Table 8, footnote (m, n, o), Table 9, footnote (m, n, o)
Added text to specify, the Follow-Up Period will consist of the Off-Tx Visit. No further visits will be conducted. The sponsor has decided to terminate survival follow-up for all subjects currently in survival follow-up. Survival follow-up data will no longer be collected after the Off-Tx Visit and after 30 days from the last dose of study drugs.	To clarify the duration of the Follow Up Period and data collection in the Follow Up Period.	• Synopsis, Study Phases • Section 9.1.3.2 • Section 9.3.3 • Section 9.5.2 Table 8, v, bb and Table 9, v, bb
Added text to clarify that subjects who undergo the Off-Tx visit will undergo safety follow-up for AEs for 30 days from the last dose of study treatment and for SAEs 90 days after the last dose or 30 days following the last dose if the	To clarify the timing of the AE and SAE collection following the Off-Tx Visit in the Follow-Up Period.	• Section 9.1

subject initiates new anticancer therapy, whichever is earlier.		
Revised the text to restart lenvatinib at least 2 weeks after major procedures.	To align with the current protocol template and the label update.	• Synopsis, Study Treatment Dose Modification • Section 9.4.1.1.1
Updated the Dose-Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab.	The dose modification and toxicity management guidelines for immune-related adverse events and table were updated as requested by the US FDA in an effort to harmonize the presentation of safety information across all FDA-approved PD-1/L1 antibody prescribing information.	• Synopsis, Study Treatment Dose Modification • Section 9.4.1.2 Table 4
Added text for the Management of QT Prolongation.	To align with the current protocol template and the label update.	• Section 9.4.1.1.8
Added text for Management of Osteonecrosis of the Jaw.	To align with the current protocol template and the label update.	• Section 9.4.1.1.9
Added text to indicate that as of Amendment 09, pre-baseline scans will no longer need to be provided for the renal cell carcinoma (RCC) cohort.	To clarify that pre-baseline scans for RCC subjects are not required.	• Synopsis, Efficacy Assessments • Section 9.5.1.3.
Added text to specify, all study-related medical or dental decisions must be made by an investigator who is a qualified physician.	To align with the current protocol template.	• Section 9.5.1
Added oral examinations to be conducted during physical examinations prior to and periodically during lenvatinib treatment.	To align with the current protocol template.	• Synopsis, Safety • Section 9.5.1.2.1 • Section 9.5.1.5 • Section 9.5.1.5.5 • Section 9.5.2, Table 8 and Table 9, footnote (e)
Added text for collecting and reporting death. All deaths will be collected for 30 days following the last dose of study treatment and	To revise the time in the Follow-Up Period when death events will be collected.	• Section 9.5.1.5.1

reported on the Survival Case Report Form.		
Added text for monitoring QT prolongation and the method used to calculate QTc.	To align with the current protocol template.	• Section 9.5.1.5.6
Added text to clarify investigator assessment will be based upon institutional reports.	To align with the current protocol template.	• Section 9.5.1.5.7
Revised the frequency of MUGA/ECHO scans in the Phase Ib and Phase 2 Extension Phase to "as clinically indicated".	To align with the standard of care for treatment of patients in the disease populations.	• Section 9.5.2, Table 8, footnote (z), Table 9, footnote (y)
Revised the frequency of Weight and Body temperature in the Phase 1b and Phase 2 Extension Phase to "as clinically indicated".	To align with the standard of care for treatment of patients in the disease population.	• Section 9.5.2, Table 8, footnote (d), Table 9, footnote (d)
Minor typographical and grammatical changes were made throughout the document.	To correct or clarify text.	• Throughout

Amendment 08
Date: 24 Aug 2020

Change	**Rationale**	**Affected Protocol Sections**
Scans acquired after data cutoff for final efficacy analysis will no longer be sent to the imaging core lab (ICL).	Independent imaging review no longer required after final efficacy analysis data cut.	Synopsis, Efficacy Assessments Section 9.5.1.3
Added text for the renal cell cancer (RCC) cohort subjects that were pretreated with anti-PD-1/PD-L1 monoclonal antibody (mAb), to allow collection of available pre-Baseline scans that demonstrate previous progression, and will be sent to an ICL.	To allow for potential independent imaging review (IIR) of pre-Baseline scans for confirmed progression on the prior anti-PD-1/PD-L1 mAb.	Synopsis, Efficacy Assessments Section 9.5.1.3

The pharmacokinetic (PK)/pharmacodynamics (PD) analyses are removed.	PK/PD analyses are not an objective of this study.	Synopsis, Pharmacokinetic-Pharmacodynamic; Statistical Methods Section 9.7.1.1.3, Section 9.7.1.2, Section 9.7.1.7.1, and Section 9.7.1.7.2
The dose-normalized PK profile for lenvatinib in combination with pembrolizumab from this study will be compared graphically to that from subjects with different tumor types from completed studies of those receiving lenvatinib monotherapy.	To compare the PK profile from this combination treatment study with that from lenvatinib monotherapy to assess any drug–drug interaction between lenvatinib and pembrolizumab.	Synopsis, Pharmacokinetic; Statistical Methods Section 9.7.1.7.1
To clarify that the blood sample for peripheral blood mononuclear cells (PBMCs) and plasma isolation was to be collected from Amendment 01.	To clarify when this sample collection was implemented.	Section 9.5.1.4.2

Revision to Amendment 07
Date: 19 Apr 2019

Change	**Rationale**	**Affected Protocol Sections**
Added text to indicate that the renal cell carcinoma (RCC) cohort will be expanded from approximately 120 to approximately 145 evaluable subjects.	To permit approximately 100 evaluable subjects in the RCC subset that were previously treated with an anti-PD-1/PD-L1 treatment to be enrolled.	Clinical Protocol Synopsis, Section 9.1, Figure 2 and footnotes, Section 9.3, Section 9.7.2, and Section 9.7.3.
Inclusion Criterion 1, PD-1 Treatment Progression sub-criterion (b), modified as follows: b) Has demonstrated disease progression after PD-1/PD-L1 as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessmen no less than	To clarify that the initial RECIST v1.1 evidence of PD is to be confirmed by a second assessment in all subjects.	Clinical Protocol Synopsis, Section 9.1, Section 9.3.1

4 weeks from the date of the first documented PD.		
Added Table 13 and information to show the 95% confidence intervals (CI) for a range of observed ORRs from 25% to 45% in RCC subjects who had previously failed an anti-PD-1/PD-L1 treatment with a sample size of 100 subjects.	To show how the increase in sample size following the second interim analysis improves the 95% CI of the ORR	Section 9.7.2
Added text to indicate that the regimen with an anti-PD-1/PD-L1 mAb must be the most recent therapy	To clarify that "*the regimen with an anti-PD-1/PD-L1 mAb must be the most recent therapy*"	Clinical Protocol Synopsis, Section 9.1, Section 9.3.1
Minor editorial changes	To correct errors or clarify text.	Throughout protocol

Revision to Amendment 06
Date: 31 Jul 2018

Change	**Rationale**	**Affected Protocol Sections**
Minor editorial changes	To correct errors or clarify text, and to update study personnel	Throughout, and Protocol Signature Page
Increased the planned number of investigational sites to up to 25 sites in the United States (US) and European Union (EU).	To accommodate expansion of enrollment of the subset of subjects with renal cell carcinoma (RCC) who progressed after treatment with an anti-PD-1/PD-L1 monoclonal antibody (mAb).	Clinical Protocol Synopsis, Section 6, and Section 9.3.
Added text to indicate that the RCC cohort will be expanded to approximately 120 evaluable subjects.	To clarify that, as of Amendment 06, "approximately" 120 subjects, rather than "up to" 120 subjects with RCC (per Amendment 05), would be enrolled.	Clinical Protocol Synopsis, Section 9.1, Figure 2 footnote, Section 9.3, Section 9.7.2, and , and Section 9.7.3.

Assessments of tumor response based on independent imaging review (IIR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) for subjects with endometrial cancer and for subjects with RCC were added to the exploratory objectives, and exploratory efficacy assessments were added to the corresponding exploratory endpoint.	To add the standard RECIST v1.1 analysis of tumor assessment for subjects with RCC.	Clinical Protocol Synopsis, Section 8.3, Section 9.7.1.1.3, and Section 9.7.1.6.3.
Modified the Phase 2 expansion of enrollment in the RCC cohort to cap the number of treatment-naïve subjects at approximately 12 and to increase the number of previously treated subjects who progressed on or after treatment with an anti-PD-1/PD-L1 agent to 33.	To clarify that treatment-naïve subjects will no longer be enrolled and to increase enrollment of previously treated subjects who progressed after treatment with an anti-PD-1/PD-L1agent to obtain additional efficacy and safety data in this subset of patients.	Clinical Protocol Synopsis, Section 9.1, Figure 2, Section 9.3.1, Section 9.7.2, and Section 9.7.3.
Revised Exclusion Criterion 12 text to clarify that subjects who have had an allogenic tissue/solid organ transplant are to be excluded.	To update text in accordance with current pembrolizumab label.	Clinical Protocol Synopsis and Section 9.3.2.
Added text to indicate that the second interim analysis will include the 11 treatment-naïve RCC subjects included in the first interim analysis plus the 45 additional RCC subjects enrolled after completion of the first interim analysis.	To clarify which subjects with RCC will be included in the second interim analysis.	Clinical Protocol Synopsis, Section 9.1, Section 9.7.2, and Section 9.7.3.
Specified that the decision to continue to expand enrollment of the subset of RCC subjects who progressed on or after previous treatment with an anti-PD-1/PD-L1 agent will be based on review of efficacy and safety data from the second interim analysis.	To clarify that further expansion of the RCC cohort based on results of the second interim analysis would be limited to previously treated subjects with RCC who progressed on or after anti PD-1/PD-L1 treatment.	Clinical Protocol Synopsis, and Section 9.7.2, and Section 9.7.3.

Specified that available mutation status, including mismatch repair (MMR) or microsatellite instability (MSI) status, will be collected on the electronic case report form (eCRF).	To ensure that MMR and MSI data are collected on the eCRF for possible evaluation.	Clinical Protocol Synopsis and Section 9.5.1.4.2
Updated Table 12 for the second interim analysis in the RCC cohort.	To adjust the objective response rate (ORR) estimate and 2-sided 95% confidence interval of the ORR for the second interim analysis based on updated enrollment numbers.	Section 9.7.2
Updated reference list	To delete references that were no longer cited in the protocol.	Section 10

Revisions to Amendment 05
Date: 22 Dec 2017

Change	Rationale	Affected Protocol Sections
Minor editorial changes	To correct errors or clarify text.	Throughout
Abbreviation list was updated.	To ensure updated abbreviation list.	List of abbreviations and definition of terms
In the Phase 2 expansion, added the option to increase enrollment in the renal cell carcinoma (RCC) cohort to up to 120 subjects based on the results of 2 interim analyses, after 22 and 56 subjects have sufficient follow-up to be evaluated for response. Added text to specify that after the first interim analysis, approximately 20 treatment- naïve subjects and an additional 25 previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 monoclonal antibody (mAb) will be enrolled.	To obtain additional efficacy and safety data for the combination at the recommended Phase 2 dose (RP2D) for these defined RCC subject subsets.	Clinical Protocol Synopsis, Section 9.1, Section 9.7.2, Section 9.7.3

As part of the second interim analysis, whether the cohort will be further expanded to 120 subjects, and the proportion of subjects remaining to be enrolled who are treatment naïve vs those having 1 or 2 previous lines of therapy will be decided based on clinical review of both efficacy and safety data.		
Added exploratory objective, endpoint, and efficacy assessment to evaluate tumor response in subjects with RCC using independent imaging review (IIR).	IIR assessment of tumor response for RCC subjects has been added to obtain unbiased independent review results to support investigator assessments and regulatory authority expectations.	Clinical Protocol Synopsis, Section 8.3, Section 9.5.1.3, Section 9.7.1.1.3, Section9.7.1.6.3
Revised Figure 2 – Study Design.	To reflect revised study design with the expansion of the RCC cohort.	Section 9.1 (Figure 2)
Number of subjects was updated to reflect that the RCC cohort may be further expanded to up to 120 evaluable subjects.	To reflect the changes in sample in the RCC cohort.	Clinical Protocol Synopsis (Number/Type of Subjects), Section 9.3
Added new text to Inclusion Criterion 1 so as of Amendment 05, for the RCC cohort, subjects are either treatment naïve or must have progressed on treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. For the previously treated RCC subjects, it was specified that PD-1 treatment progression is defined by meeting all of the following criteria: a) Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb b) Has demonstrated disease progression after PD-1/PD-L1 as defined by RECIST v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression.	To ensure there is a consistent application of the desired pre-study disease progression after prior anti-PD-1/PD-L1 definition in this previously treated RCC subset and to decrease the risk of including subjects with pseudo-progression.	Clinical Protocol Synopsis, Section 9.1, Section 9.3.1.

c) Progressive disease has been documented within 12 weeks from last dose of anti-PD-1/PD-L1 mAb (refractory disease) or ≥12 weeks from last dose of anti-PD-1/PD-L1 mAb (late relapses).		
Modified Inclusion Criterion 1 for Phase 2 of the study to specify that previously treated subjects must have progressed pre-study. Also, it is required that subjects have received no more than 2 prior lines of therapy. Additional text stating "unless discussed with the sponsor" was deleted.	To clarify that all previously treated subjects must have progressed pre-study to be eligible for enrollment in Phase 2. The rationale for the deletion is that no subjects who have received more than 2 prior lines of therapy will be permitted into the study.	Clinical Protocol Synopsis, Section 9.3.1
Wording of Exclusion Criterion 17 modified to clarify that the exclusion of prior treatment with any anti-PD-1 or anti-PD-L1 agent does not apply for the previously treated RCC subset where prior treatment with one regimen containing an anti-PD-1/PD-L1 mAb is required. Criterion 17 was also amended to emphasize that there will be "no exceptions" for prior lenvatinib treatment.	To clarify that the exclusion does not apply for this defined previously treated RCC subject subset.	Clinical Protocol Synopsis, Section 9.3.2
Added text to clarify that "Treatment cycles will be counted continuously regardless of dose interruptions."	To provide a more consistent definition when treatment cycles are numbered or tabulated.	Clinical Protocol Synopsis, Section 9.4.1.1, Section 9.4.5, and to Table 8 and Table 9 footnote 'b'.
Updated and replaced the pembrolizumab 200 mg dose justification.	Updated from Merck pembrolizumab standard protocol template language.	Section 7.2
The pembrolizumab dose modification table was replaced with an updated table.	Updated from Merck pembrolizumab standard protocol template language.	Clinical Protocol Synopsis and Section 9.4.1.2, Table 4
Updated treatment guidelines for Grades 3 or 4 infusion reaction.	Updated from Merck pembrolizumab standard protocol template language.	Section 9.4.1.2.1, Table 5
Updated supportive care guidelines for pembrolizumab.	Updated from Merck pembrolizumab standard protocol template language.	Section 9.4.1.2.1
Added collection of Karnofsky Performance Status at Screening for RCC subjects only.	To be able to retrospectively apply the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model criteria to determine each	Section 9.5.1.1, Table 8, Table 9 Appendix 8 was added

	subject's IMDC prognostic risk group (Favorable, Intermediate, or Poor Risk) for RCC subjects for future reporting purposes.	
Added information in NOTE for events of clinical interest.	Updated from Merck pembrolizumab standard protocol template language.	Section 9.5.1.5.2
Updated text for definition of disease control rate (DCR) - stating that the irSD duration should be ≥5 weeks (previously mentioned as minimum duration from CID1 to irSD ≥5 weeks).	To standardize definition for DCR.	Statistical Methods of Clinical Protocol Synopsis, Section 9.7.1.1.2
Added dataset definitions for (1) Renal Cell Carcinoma, (2) Non-Small Cell Lung Cancer, and (3) Melanoma Analysis Sets	To clarify the populations from this study that are included in each cohort's analysis set.	Statistical Methods of Clinical Protocol Synopsis, Section 9.7.1.2
Added the possibility of conducting efficacy and safety subgroup analyses for RCC cohort for treatment naïve subjects, subjects who were previously treated with an anti-PD-1/PD-L1 therapy, and subjects who were previously treated without an anti PD-1/PD-L1 therapy.	To evaluate the efficacy and safety in these subsets of patients.	Clinical Protocol Synopsis (Efficacy Analyses, Safety Analyses), Section 9.7.1.6 (Efficacy), Section 9.7.1.8 (Safety)
Clarified that adverse events will be summarized by subgroups (age, race, and sex), if necessary.	The words "if necessary" were added to clarify that this subgroup analysis would performed if requested.	Section 9.7.1.8.2
Added sample size rationale for the RCC cohort expansion.	To elucidate statistical ramifications of the selected sample sizes.	Clinical Protocol Synopsis (Sample Size Rationale), Section 9.7.2, Section 9.7.3 Table 12 was added
Revised link to updated Keytruda Package Insert/SmPC.	To ensure most recent package insert is referenced in the protocol.	Section 10 (References), Section 12 (Appendix 7)
Revised link to updated LENVIMA and KISPLYX Package Inserts/SmPCs.	To ensure most recent package insert is referenced in the protocol.	Section 10 (References)
Reference list was updated to add additional references cited in Section 9.5.1.1.	To add references cited in the protocol.	Section 10 (References)
Removed citation to "David, et al., in press."	To correct citation error.	Section 7.1.2

Revisions to Amendment 04
Date: 23 May 2017

Change	Rationale	Affected Protocol Sections
Added name and address of Eisai Ltd as sponsor for the European Union (EU), and added EudraCT number to Title Page.	To accommodate opening of sites in the EU to enrollment.	Section 1
Added text to indicate that the study must also be conducted in accordance with the European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC.	To accommodate opening of sites in the EU to enrollment.	Section 5.2
Revised number of study sites from 5 in the US to up to 10 in the US and EU.	To update number of study sites to accommodate opening of sites in the EU to enrollment.	Clinical Protocol Synopsis and Section 9.3
Revised the definition of the end of study to: the time of data cutoff for the final analysis or the time of last subject/last treatment, whichever occurs later.	To reflect the most recent definition of end-of-study in the protocol template.	Section 5.1 and Section 9.1
Inclusion Criterion 1 modified as follows: • Phase 2: Histologically and/or cytologically confirmed metastatic selected solid tumor types with 0-2 prior lines of systemic therapy (unless discussed with the sponsor).	To clarify Inclusion Criterion 1 for subjects enrolling in Phase 2 of the study.	Clinical Protocol Synopsis, Section 9.3.1
Inclusion Criterion 11 modified to clarify steroid washout requirements.	To clarify that subjects with brain metastases at baseline must be off steroids for at least 28 days before starting study treatment.	Clinical Study Synopsis and Section 9.3.1
Inclusion Criterion 12 contraceptive language was modified.	Contraceptive language was modified to ensure compliance with current lenvatinib safety information.	Clinical Study Synopsis and Section 9.3.1
Changed title of lenvatinib dose reduction recommendation table, and added text in the footnote to specify that a discussion with the sponsor is required to resume lenvatinib treatment if it is interrupted for more than 21 days due to treatment-related toxicity.	To clarify that dose reduction recommendations for lenvatinib are for treatment-related toxicity and to clarify that a discussion with the sponsor to reinstate lenvatinib treatment after a 21-day interruption is only required if the interruption is due to lenvatinib-related toxicity.	Clinical Protocol Synopsis, Section 9.4.1.1.1, Table 2, and Table 3
Revised text to clarify that brain scans must be performed for all subjects, including those with head	To clarify that brain scans must be performed for all subjects including those with HNSCC.	Clinical Protocol Synopsis, Section 9.5.1.3, Table 8, and Table 9

and neck squamous cell carcinoma of the head and neck (HNSCC), at Screening, when clinically indicated, and to confirm immune-related complete response (irCR) within 1 week of response.		
Revised text to clarify that bone scans must be performed for all subjects, except HNSCC subjects, at Screening, every 24 weeks, when clinically indicated, and at confirmation of irCR. Also, added text to indicate that if a bone scan is required, and the timing doesn't coincide with a scheduled computed tomography (CT)/ magnetic resonance imaging (MRI) timepoint, it should be performed at the closest scheduled CT/MRI timepoint.	To clarify the timing of performance of bone scans.	Section 9.5.1.3, Table 8, and Table 9
Revised background information on pembrolizumab.	Updated Merck pembrolizumab standard protocol template language.	Section 7.1.1
Added and updated approved indications for lenvatinib and pembrolizumab in the US and EU, updated the lenvatinib label reference, and added references for Summary of Product Characteristics for lenvatinib and pembrolizumab.	To add relevant background information for EU sites and investigators and to update approved indications and label references.	Section 7.1.1, Section 7.1.2, Section 10, and Appendix 7
Revised text for management of proteinuria.	To ensure consistency in the management of proteinuria among the lenvatinib clinical studies.	Section9.4.1.1.3 and Section 9.5.2.1, (Table 9)
Added requirement that pembrolizumab treatment is to be discontinued for subjects with recurrent Grade 2 pneumonitis.	Updated Merck pembrolizumab standard protocol template language.	Clinical Protocol Synopsis and Section 9.4.1.2 (Table 4).
Added additional background information on pembrolizumab.	Updated Merck pembrolizumab standard protocol template language.	Section 9.4.2.2.
Management of hypertension section clarified that on the second and third reoccurrence of hypertension that lenvatinib administration should be interrupted, the dose should be reduced and only restarted once the subjects has been on a stable regimen of antihypertensive therapy and acceptable blood pressures are recorded.	Change made to ensure consistency in the management of hypertension across lenvatinib clinical studies.	Section 9.4.1.1.2

Revised and clarified text for measurement of blood pressure (BP) as follows: • defined assessment of BP as the mean of 3 measurements at least 5 minutes apart, • clarified that subjects with elevated BP (≥140 mmHg systolic or ≥90 mmHg diastolic) were to have 2 assessments at least 1 hour apart, and • clarified that subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 1 and Day 15 or more frequently, as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months	To ensure consistency in BP measurements among the lenvatinib clinical studies.	Section 9.5.1.5.4 and Section 9.5.2.1 (Table 9)
Added blood sample collection for potential gene expression analysis.	To obtain samples from Phase 2 subjects for possible gene expression analysis.	Clinical Protocol Synopsis, Section 9.5.1.4.2, Section 9.5.2.1, Table 9
Added text to footnote b to refer the reader to management of hypertension section for more specific dose modification guidelines for hypertension.	Clarification, since more specific dose modification guidelines for hypertension is contained in Section 9.4.1.1.2.	Clinical Protocol Synopsis, Section 9.4.1.2 (Table 2, Footnote b)
Revised New York Heart Association (NYHA) Cardiac Disease Classification.	To specify that the NYHA Classification applies to only subjects with heart failure and to clarify the Class categories.	Appendix 4
Added the following text to 9.5.1.1: "FIGO grade (Creasman, 2009) will be collected from all endometrial carcinoma subjects if available."	To obtain information on the stage of endometrial cancer from the subjects in Study -111. These data will be used to see if they have prognostic value when lenvatinib plus pembrolizumab are co-administered.	Section 9.5.1.1 and reference added to 10 REFERENCE LIST.
Added the following text: "Patients can receive up to 35 treatments (approximately 2 years) with pembrolizumab."	Updated Merck pembrolizumab standard protocol template language.	"Overall Design" element of both the Clinical Protocol Synopsis and Section 9 Investigational Plan, as well as in footnotes z. and aa. of Table 8 and Table 9 respectively, of Section 9.5.2.1 Schedule of Procedures/ Assessments.

Revisions to Amendment 03
Date: 26 Oct 2016

Change	Rationale	Affected Protocol Sections
Changed "urothelial cancer" to "urothelial carcinoma", and "endometrial cancer" to "endometrial carcinoma" throughout the protocol	Change made for consistency of terminology with Amendment 02.	Throughout the protocol.
Added the recommended Phase 2 dose of the combination determined during Phase 1	To clarify dosage of the combination to be used in Phase 2.	Clinical Protocol Synopsis
Added exploratory objective and endpoint to evaluate tumor response in the endometrial carcinoma cohort using independent imaging review (IIR).	IIR assessment of tumor response results added to obtain unbiased results to support investigator assessments and potential regulatory filing.	Clinical Protocol Synopsis, Section8.3, Section 9.7.1.1.3, Section 9.7.1.6.3
In the Phase 2 expansion, added the option to increase enrollment in the endometrial carcinoma cohort to up to 120 subjects based on the results of 2 interim analyses after 21 and 60 subjects have sufficient follow-up to be evaluated for response.	To obtain additional efficacy and safety data for the combination at the RP2D (lenvatinib 20 mg/day plus pembrolizumab 200 mg IV Q3W) in endometrial carcinoma based on clinical results.	Clinical Protocol Synopsis, Section 9.1, Section 9.7.2, Section 9.7.3
Inclusion criterion 1 modified to add requirement for previous therapy for the non-small cell lung cancer and melanoma cohorts	To add a criterion for the non-small cell lung cancer and melanoma cohorts, considering the current treatment practice.	Clinical Protocol Synopsis, Section 9.3.1
Exclusion criterion 20 modified to clarify that subjects with a history of non-infectious pneumonitis that required steroids and subjects with current pneumonitis are to be excluded.	To ensure exclusion of subjects with non-infectious pneumonitis requiring steroid treatment, and subjects with current pneumonitis based on safety information from ongoing combination pembrolizumab clinical trials.	Clinical Protocol Synopsis, Section 9.3.2
Added text to separate dose modification instructions for lenvatinib- and pembrolizumab-related toxicity.	To further separate and clarify dose modification instructions for lenvatinib-related and pembrolizumab-related toxicity	Clinical Protocol Synopsis, Section 9.4.1.1.1
Added blood sample collection for potential pharmacogenomic analysis.	To obtain samples from Phase 2 subjects for possible pharmacogenomic analysis.	Clinical Protocol Synopsis, Section 9.5.1.4.2, Section 9.5.2.1, Table 9
Updated list of approved indications for pembrolizumab in the US.	To provide latest information on the approved indications for pembrolizumab in the US.	Section 7.1.1

Text added to clarify the definition of a prior systemic therapy for enrollment in Phase 2.	Clarification of the definition of prior systemic therapy for the study sites.	Section 9.4.7
Added collection of peripheral blood mononuclear cells (PBMCs) to Schedule of Assessments	To define the term PBMC and to clarify timing of collection of PBMCs.	Section 9.5.2.1, Table 9
Modified efficacy analysis plan to include a possible sensitivity analysis of the combination of lenvatinib + pembrolizumab comparing treatment-naïve subjects versus subjects with prior lines of systemic therapy.	To evaluate selected efficacy parameters in treatment-naïve subjects versus previously treated subjects.	Section 9.7.1.6
Safety analysis plan modified to include a possible evaluation of safety of the combination of lenvatinib + pembrolizumab in treatment-naïve subjects versus subjects with prior lines of systemic therapy.	To evaluate selected safety parameters in treatment-naïve subjects versus previously treated subjects.	Section 9.7.1.8

Revisions to Amendment 02
Date: 30 Mar 2016

Change	**Rationale**	**Affected Protocol Sections**
Limited renal cell carcinoma to "predominantly clear cell" renal cell carcinoma and clarified that subjects with uveal melanoma were excluded. Changed endometrial cancer and urothelial cancer to endometrial carcinoma and urothelial carcinoma, respectively.	To clarify that only subjects with "predominantly clear cell" renal cell carcinoma, melanoma (excluding uveal melanoma), endometrial carcinoma, and urothelial carcinoma are allowed in these 4 tumor type cohorts.	Clinical Protocol Synopsis Inclusion Criteria and Section 9.3.1 - Inclusion Criterion 1.
Exclusion Criterion 17 modified to allow, for the melanoma and NSCLC cohorts only, previous treatment by one PD-1, anti-PD-L1, or anti-PD-L2 agent. Previous treatment with a PD-1, anti-PD-L1, or anti-PD-L2 agent is still excluded for the other 4 cohorts.	To increase the rate of enrollment in the melanoma and NSCLC cohorts since (1) programmed death receptor-1 (PD-1)-blocking antibodies have been approved in these 2 indications and (2) the study sites participating in this protocol are tertiary cancer care centers which typically will not treat first-line subjects.	Clinical Protocol Synopsis Exclusion Criteria and Section 9.3.2 - Exclusion Criterion 17.
For asymptomatic Grade ≥3 elevations of amylase and lipase, the sponsor's medical monitor can authorize continued treatment of the subjects.	Some of the study investigators noted that asymptomatic Grade 3 or 4 elevations in amylase and lipase are not uncommon in subjects receiving VEGF/TKIs and Checkpoint inhibitors. They	Clinical Protocol Synopsis - Study Treatment Dose Modifications for Lenvatinib and Pembrolizumab, Section 9.4.1.1.1, Table 2 Dose Modifications for Lenvatinib,

	indicated that subjects will be lost unnecessarily (since the investigators cannot wait until amylase resolves to Grade 0-1, they have to take subjects off) while subjects are asymptomatic. They also noted that, in other studies with VEGF/TKIs and Checkpoint inhibitors, the protocol includes the language that such subjects can continue treatment if asymptomatic and after discussion with the sponsor.	Section 9.4.1.2, Table 4 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events
Added general guidelines for holding periods of lenvatinib due to minor and major procedures.	To align this study with earlier Eisai protocols.	Clinical Protocol Synopsis - Study Treatment Dose Modification for Lenvatinib and Section 9.4.1.1.1 Dose Modifications for Lenvatinib
Mandatory requirement for freshly obtained biopsies from subjects in the NSCLC cohort changed to say that all efforts should be made to obtain the fresh biopsies.	Based on advice from the study investigators that study enrollment will be difficult with mandatory requirements for freshly obtained biopsies.	Clinical Protocol Synopsis - Pharmacodynamic/ Pharmacogenomic and Section 9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker, Assessments, and Table 9 - Phase 2 – Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases
Revised Pembrolizumab's [Keytruda (US)] list of approved indications by country.	Requested by Merck following a pembrolizumab labeling change in February 2016.	Section 7.1.1 PD-1 Inhibitors and Pembrolizumab
Paragraph relating to reporting of events of clinical interest (ECI) as serious within 24 hours removed.	Merck notified Eisai that the ECI guidance document has been retired and it no longer requires ECI to be reported as serious within 24 hours.	Section 9.5.1.5.2 Serious Adverse Events and Events Associated With Special Situations

Revisions to Amendment 01

Date: 14 Jan 2016

Change	Rationale	Affected Protocol Sections
Exploratory Objectives Update to align with the planned biomarker analysis in the exploratory objective	Add supporting languages in order to make the planned analysis clear.	• Clinical Protocol synopsis • Section 8.3
Inclusion Criteria #1 Add an exception that subject who has not received nivolumab	Nivolumab and pembrolizumab have been approved for melanoma and NSCLC and may be approved for additional tumor	• Clinical Protocol synopsis • Section 9.3.1

or pembrolizumab can be enrolled in this study even if nivolumab or pembrolizumab is an approved therapy.	types. Although these are "approved therapies" since pembrolizumab is in the same class of drugs as nivolumab an Investigator could still enroll subjects with these tumors into Phase 1b in lieu of the approved nivolumab or pembrolizumab therapy.	
Inclusion Criteria #15 Change to note that either "Archival tumor tissue or a newly obtained biopsy must be available prior to the first dose of study drug for biomarker analysis. Patients with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the sponsor."	Allows subjects without sufficient archival tissue for biomarker analysis an alternate path for enrollment into the study. Also, provide the exception in case of patients with inaccessible tumors upon consultation and agreement by the sponsor.	• Clinical Protocol synopsis • Section 9.3.1 • Section 9.5.1.4.2 • Section 9.5.2.1, Tables 8 and 9
Exclusion Criteria #2 Change to "Subjects must have recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy."	Recovery from major surgery is dependent upon the extent of the surgery as well as the physical state of the individual. The revised criterion allows the Investigator to determine the appropriate recovery period for each patient dependent upon that patient's well-being.	• Clinical Protocol synopsis • Section 9.3.2
Exclusion Criteria #21 Change to "Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted."	Updated by the latest pembrolizumab protocol template provided by Merck to make it specified. ("Pembrolizumab Text for Eisai PN146 27-Oct-2015.")	• Clinical Protocol synopsis • Section 9.3.2
Update Dose Modification Guideline for Pembrolizumab-Related Adverse Events	Updated by the latest pembrolizumab protocol template provided by Merck ("Pembrolizumab Text for Eisai PN146 27-Oct-2015").	• Clinical Protocol synopsis • Section 9.4.1.2
Update the introduction of pembrolizumab	Updated by the latest pembrolizumab protocol template provided by Merck. ("Pembrolizumab Text for Eisai PN146 27-Oct-2015").	• Section 7.1.1
Delete the description of Events of Clinical Interest (ECI) Guidance Document	Merck notified Eisai that the ECI guidance document has been retired.	• Section 9.4.1.2 • Section 9.5.1.5.2 • Section 9.5.4.1 • Section 9.4.1.2.1

Reporting of ECI is no longer required		• Section 9.5.4.3.2
Laboratory Measurements: Delete the description of retrospective analysis for thyroid antibodies	Aliquots of the samples will not be stored for potential retrospective analysis for thyroid antibodies.	• Section 9.5.1.5.3, Table 7
Clarify the planned analysis in Phase 2	The change clarifies that there is no statistical analysis based Interim Analysis. Sponsors and Investigators enrolling patients into the cohort will discuss the totality of the efficacy and safety data from the first 10 subjects and develop a consensus on whether expanding the cohort to 20 subjects is warranted.	• Section 9.7.3

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. E7080, MK-3475

Name of Active Ingredient: Lenvatinib and Pembrolizumab

Study Protocol Title:

A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors

Investigators

To be determined

Sites

Up to 25 centers in the United States and the European Union (EU).

Study Period and Phase of Development: Phase 1b/2

Objectives

Primary Objectives

- Phase 1b – Determination and confirmation of the maximum tolerated dose (MTD):
  - To determine and confirm the MTD for lenvatinib in combination with 200 mg (intravenous [IV], every 3 weeks [Q3W]) pembrolizumab in subjects with selected solid tumors.
- Phase 2 – Expansion In Selected Tumor Types (Expansion):
  - To evaluate the objective response rate (ORR) as of Week 24 ($ORR_{(Week\ 24)}$: complete response [CR] + PR [$CR_{(Week\ 24)}$ + $PR_{(Week\ 24)}$]) of lenvatinib in combination with pembrolizumab in each of the cohorts, using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).

Secondary Objectives (for both Phase 1b and 2)

- To assess:
  - Tolerability and safety profile of lenvatinib in combination with pembrolizumab
  - ORR by irRECIST of lenvatinib in combination with pembrolizumab in subjects with solid tumors
  - Progression-free survival (PFS) by irRECIST
  - Overall survival (OS)
  - Duration of response (DOR) by irRECIST
  - Disease control rate (DCR: CR + PR + stable disease [SD]) by irRECIST
  - Durable stable disease rate (durable SD [SD ≥23 weeks]) by irRECIST
  - Clinical benefit rate (CBR: CR, PR + durable SD) by irRECIST
  - the pharmacokinetic (PK) profile of lenvatinib during combination treatment.

Exploratory Objectives

- To explore tumor response (eg, PR, CR, SD, PD) based on modified RECIST 1.1 assessments
- To explore tumor response in subjects with endometrial carcinoma (EC) and renal cell carcinoma based on independent imaging review (IIR) using irRECIST, modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and RECIST 1.1.

- To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of lenvatinib in combination with pembrolizumab:
  a. To evaluate the relationship between programmed cell death protein 1 ligand (PD-L1) expression levels and other relevant biomarkers (eg, tumor infiltrating lymphocytes, T-cell repertoire, ribonucleic acid [RNA] signature profiles) in tumor samples and anti-tumor activity of lenvatinib in combination with pembrolizumab.
  b. To evaluate differences in tumor tissue characteristics in biopsies taken post treatment with lenvatinib in combination with pembrolizumab versus baseline.

Study Design

Overall Design:

This is a multicenter, open-label study with a Phase 1b and a Phase 2 component.

Phase 1b - MTD: This phase will determine and confirm the MTD of lenvatinib in combination with pembrolizumab. Subjects in Phase 1b will have one of the following tumors: non-small cell lung cancer (NSCLC), renal cell carcinoma, EC, urothelial carcinoma (UC), squamous cell carcinoma of the head and neck, or melanoma. Ten to 30 subjects will be enrolled in Phase 1b. The dose of 1 of the 2 study drugs, pembrolizumab, will not change during the MTD phase, while the second study drug, lenvatinib, will start at 24 mg and then be reduced, if necessary, to either 20 mg or 14 mg.

Phase 2 - Expansion: Subjects will be assigned by tumor type to 1 of 6 cohorts to receive the MTD, which was established as the recommended Phase 2 dose (RP2D) in the Phase 1b portion of this study, (lenvatinib 20 mg/day orally + pembrolizumab 200 mg every 3 weeks [Q3W] IV) to assess the safety and efficacy of the combination in the selected tumor-types. Each cohort will consist of subjects with 1 of the tumor types listed in the Phase 1b section above.

For subjects in Phase 1b and Phase 2, toxicity will be managed by treatment interruption, dose reduction and/or treatment discontinuation in accordance with prespecified dose modification instructions. Treatment will continue until disease progression, development of unacceptable toxicity, subject choice, withdrawal of consent, completion of 35 treatments (approximately 2 years) with pembrolizumab, lost to follow up or discontinuation of this study by the sponsor.

Patients can receive up to 35 treatments (approximately 2 years) with pembrolizumab. Subjects who discontinue pembrolizumab for any reason and are still receiving lenvatinib study drug will be transitioned to commercial lenvatinib if local country regulations permit. Subjects who discontinue pembrolizumab after 35 treatments may continue treatment with lenvatinib alone unless any other criteria above apply.

Phase 1b - MTD: Dosing will begin at the full dose of both drugs due to the well-established safety profiles of lenvatinib and pembrolizumab, the non-overlapping mechanisms of action, and the desire to treat patients at doses shown to be effective in previous studies. Lower dose levels of lenvatinib will be explored as necessary depending on observed toxicity. Phase 1b will begin with Dose Level 1; lenvatinib 24 mg/day orally and pembrolizumab 200 mg every 3 weeks IV will be administered to subjects with selected solid tumors on a 21-day treatment cycle. Two dose de-escalation steps are included: Dose Level 2 (lenvatinib 20 mg/day orally + pembrolizumab 200 mg Q3W, IV) and Dose Level 3 (lenvatinib 14 mg/day orally + pembrolizumab 200 mg Q3W, IV). For determination of MTD, only dose limiting toxicities (DLTs) during the first cycle of treatment will be assessed. The determination of the DLT will be made jointly by the sponsor and investigators after safety data from each dose level have been reviewed.

If 0 of 3 subjects in a given dose level cohort experiences a DLT, then 7 more subjects will be enrolled into that dose level to confirm the MTD. If 1 of 3 subjects has a DLT, then 3 more

subjects will be enrolled into that dose level for a total of 6 subjects. If only 1 of these 6 subjects has a DLT, then 4 more subjects will be enrolled into that dose level to confirm the MTD.

If 2 or more subjects at a dose level experience a DLT, then, following consultation with the PIs the study will proceed with enrollment in the next defined lower dose (Dose Level 2 or 3), with dose reduction of lenvatinib to 20 or 14 mg once a day, respectively, in combination with 200 mg pembrolizumab Q3W.

For confirming the MTD, DLTs and intolerable toxicities (that cannot be managed with dose interruption and/or reduction) during the first cycle of treatment for the 10 evaluable subjects at that dose level will be assessed. The MTD will be confirmed if no more than 3 subjects experience DLTs during the first 3 weeks (Cycle 1) of treatment. If the MTD is not confirmed at a dose level, then enrollment will proceed to the next lower dose level. The sponsor and investigators will review all subjects' safety and clinical data to jointly determine the RP2D of the combination of lenvatinib with pembrolizumab.

If 2 or more subjects have a DLT in Dose Level 3, enrollment in the study will stop.

A DLT is defined as any of the following:

- Any of the hematological or nonhematological toxicities noted in the table below considered to be at least possibly related to lenvatinib and/or pembrolizumab occurring during Cycle 1.
- Failure to administer ≥75% of the planned dosage of lenvatinib as a result of treatment-related toxicity during Cycle 1.
- Subjects who discontinue treatment due to treatment-related toxicity.
- Greater than 2 week delay in starting Cycle 2 because of a treatment-related toxicity, even if the toxicity does not meet DLT criteria.

Dose Limiting Toxicities	
Toxicity Category	**Toxicity CTCAE Grade**
Hematologic	Grade 4 neutropenia for ≥ 7 days
	Grade 3 or Grade 4 febrile neutropenia[a]
	Thrombocytopenia <25,000/mm^3 associated with bleeding and/or that requires platelet transfusion
Other nonhematologic toxicity	Any other Grade 4 or a Grade 5 toxicity Grade 3 toxicities lasting >3 days excluding: Nausea, vomiting, and diarrhea controlled by medical intervention within 72 hours. Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab.
	Grade 3 hypertension not able to be controlled by medication
	Grade 3 or above gastrointestinal perforation
	Grade 3 or above wound dehiscence requiring medical or surgical intervention
	Any grade thromboembolic event
	Any Grade 3 nonhematologic laboratory value if: Medical intervention is required to treat the subject, or the abnormality leads to hospitalization

ANC = absolute neutrophil count, CTCAE = Common Terminology Criteria for Adverse Events v4.03.
a. Febrile neutropenia Grade 3 or Grade 4:
Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour.
Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour, with life-threatening consequences and urgent intervention indicated

Only toxicities with a clear alternative explanation (eg, due to disease progression) or transient (≤72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination can be deemed a non-DLT.

All subjects enrolled in Phase 1b will be assessed for DLTs during the DLT assessment window of Cycle 1 (Treatment Phase). Subjects who discontinue study treatment prior to completing the Treatment Phase for any reason other than DLT will be replaced. Once they complete the Treatment Phase, each subject still receiving study treatment will transition into the Extension Phase. Tumor assessments will continue during the Extension Phase. As of Amendment 09, tumor assessments will continue during the Extension Phase as per local standard of care but not less frequent than every 6 months. Tumor assessments will not be collected during the Follow-Up period of the Extension Phase.

Phase 2 - Expansion:

After the MTD is confirmed, and depending on the safety and efficacy observed, 6 cohorts will be enrolled. Each of these cohorts will enroll subjects with only 1 type of tumor (ie, NSCLC, predominantly clear cell renal cell carcinoma, EC, UC, melanoma (excluding uveal melanoma), or squamous cell carcinoma of the head and neck). Lenvatinib in combination with pembrolizumab will be administered at the RP2D. The intent is to enroll 20 subjects in each of the 6 cohorts, with possible expansion of enrollment in the endometrial and renal cell carcinoma cohorts. For all 6 cohorts, data from the first 10 subjects in each cohort will be reviewed by the sponsor and investigators. At least 3 subjects must show responses in order to determine continued enrollment to 20 evaluable subjects.

As of Amendment 3, the EC cohort may be further expanded to approximately 120 evaluable subjects. The decision to expand enrollment will be based on the efficacy results of 2 interim analyses that will take place when 21 and 60 subjects have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 21), if there are more than 3 responses, then approximately 40 additional subjects will be enrolled. At the second interim analysis (N = 60), if there are more than 12 responses, approximately 60 additional subjects will be enrolled. If there are 12 or fewer responses, the sponsor may decide whether to expand enrollment based on clinical outcome, eg, ORR and DOR.

As of Amendment 07, the renal cell carcinoma cohort may be further expanded to approximately 145 evaluable total renal cell carcinoma (RCC) subjects to allow for approximately 100 evaluable subjects who have received 1 or 2 prior therapies that included an anti- programmed cell death protein 1 (PD-1)/ PD-1 ligand 1 (PD-L1) mAb. The decision to expand enrollment will be based on the results of 2 interim analyses. The first interim analysis will take place when 22 subjects, 11 treatment naïve and 11 previously treated without an anti-PD-1/PD-L1 monoclonal antibody (mAb), have sufficient follow-up to be evaluated for response. At the first interim analysis (N=22), if there are more than 5 responses, then approximately 45 additional subjects will be enrolled. It is anticipated that the additional 45 subjects will consist of approximately 12 treatment naïve subjects enrolled under Amendment 05 and approximately 33 previously treated subjects who have received

1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 mAb. The second interim analysis will include these 45 additional subjects and the 11 treatment naïve subjects included in the first interim analysis, and will take place when these 56 subjects have sufficient follow-up to be evaluated for response. At the second interim analysis, whether the previously treated RCC subset will be further expanded will be decided based on clinical review of both efficacy and safety data.

Study Phases

The study will be conducted in 3 phases: a Pretreatment Phase, a Treatment Phase, and an Extension Phase.

The **Pretreatment Phase** will last no longer than 28 days and includes:

A Screening Period, to obtain informed consent and establish protocol eligibility, and a Baseline Period, to confirm protocol eligibility prior to treatment.

The **Treatment Phase** will begin with the administration of the first dose of study drug to the first subject in Cycle 1 and will continue in 21-day (3-week) cycles. The Treatment Phase consists of 1 treatment period as described below.

Treatment Period

Phase 1b: The Treatment Period for each subject ends after completing Cycle 1 of treatment or they discontinue early. Those subjects who discontinue study treatment in Cycle 1 transition to the Off Treatment (Off-Tx) Visit of the Follow-up Period of the Extension Phase. Those who complete Cycle 1 transition to the Treatment Period of the Extension Phase.

Phase 2: The Treatment Period for each subject ends after completing 8 cycles of treatment unless the subject discontinues early. Those who discontinue study treatment before completing 8 cycles transition to the Off-Tx Visit of the Follow-up Period of the Extension Phase. Those that complete 8 cycles transition to the Treatment Period of the Extension Phase.

Extension Phase

The Extension Phase consists of a treatment period and a follow-up period.

Treatment Period (Extension Phase): Subjects still receiving study treatment at the end of the Treatment Phase will continue to receive the same treatment. Those subjects that discontinue study treatment transition to the Off-Tx Visit of the Follow-up Period of the Extension Phase. Note that all AEs must be captured for 30 days after last dose of study treatment.

Follow-up Period (Extension Phase):

As of Amendment 9, the Follow-Up Period will consist of the Off-Tx Visit. No further visits will be conducted. The sponsor has decided to terminate survival follow-up for all subjects currently in survival follow-up. Survival follow-up data will no longer be collected after the Off-Tx Visit and after 30 days from the last dose of study drug.

The Follow-up Period consists of the Off-Tx Visit and the Follow-up Visits. The Off-Tx Visit will occur within 30 days following the last dose of study treatment. It applies to the Phase 1b subjects that discontinued study treatment early, before completing Cycle 1, and to the Phase 2 subjects who discontinued study treatment early, before completing 8 cycles. Following the completion of the Off-Tx Visit, subjects will transition to the Follow-up Period of the Extension Phase. Follow-up Visits continue as long as the study subject is alive unless the subject withdraws consent or until the sponsor terminates the study. In 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 survival and subsequent anticancer treatments. The sponsor may

decide to terminate survival follow-up anytime during the Extension Phase or when all subjects have discontinued study treatment.

Number/Type of Subjects

Phase 1b - Depending on the number of dose levels explored, the Phase 1b part of this study will enroll between 10 and 30 evaluable subjects with selected solid tumors.

Phase 2 of this study will enroll subjects in 6 cohorts. A sample size of 10 evaluable subjects will be enrolled per cohort, with the possibility of expansion to 20 evaluable subjects per cohort. As of Amendment 3 the enrollment for the EC cohort may be further expanded to approximately 120 evaluable subjects. As of Amendment 7, the enrollment for the renal cell carcinoma cohort may be further expanded to approximately 145 evaluable subjects.

Inclusion Criteria

1. Phase 1b: Histologically and/or cytologically confirmed metastatic selected solid tumor types that have progressed after treatment with approved therapies or for which there are no standard effective therapies available. If nivolumab or pembrolizumab is an approved therapy for the subject's tumor type, but the subject has not been treated with it, the Investigator may enroll the subject in this study.

   Phase 2: Histologically and/or cytologically confirmed metastatic selected solid tumor types with 0-2 prior lines of systemic therapy. If previously treated, subject has progressed after previous treatment.

   As of Amendment 03, for the NSCLC and melanoma cohorts, subjects must have progressed on or after prior treatment with one anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

   As of Amendment 05, for the renal cell carcinoma cohort, subjects are either treatment naïve or must have progressed on treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies.

   As of Amendment 06, for the RCC cohort, all subjects must have progressed on treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies, and as of Amendment 07, the regimen with an anti-PD-1/PD-L1 mAb must be the most recent therapy.

   PD-1 treatment progression is defined by meeting all of the following criteria:

   a) Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb.
   b) Has demonstrated disease progression after PD-1/PD-L1 as defined by RECIST v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented PD
   c) Progressive disease (PD) has been documented within 12 weeks from last dose of anti-PD-1/PD-L1 mAb (refractory disease) or ≥12 weeks from last dose of anti-PD-1/PD-L1 mAb (late relapses)

   Selected tumor types of both phases: NSCLC, predominantly clear cell renal cell carcinoma, EC, UC, squamous cell carcinoma of the head and neck, or melanoma (excluding uveal melanoma).

2. Life expectancy of 12 weeks or more
3. Phase 2: Measurable disease meeting the following criteria:
   - At least 1 lesion of ≥10 mm in the longest diameter for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node that is serially measurable according to irRECIST using computerized tomography/magnetic resonance imaging (CT/MRI).

- Lesions that have had external beam radiotherapy or loco-regional therapies such as radiofrequency ablation must show subsequent evidence of substantial size increase to be deemed a target lesion.

4. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1
5. 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 prior to the Cycle 1 (D1)
6. Adequate renal function defined as creatinine ≤1.5 x upper limitis of normal (ULN) or calculated creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula with creatinine levels >1.5 x ULN
7. Adequate bone marrow function:
   - Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5 x 10^3/μL)
   - Platelets ≥100,000/mm^3 (≥100 x 10^9/L)
   - Hemoglobin ≥9.0 g/dL
8. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5
9. Adequate liver function as evidenced by bilirubin ≤1.5 times the ULN and alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN). In case ALP is >3 × ULN (in the absence of liver metastases) or >5 × ULN (in the presence of liver metastases) AND the subject also is known to have bone metastases, the liver specific ALP isoenzyme must be separated from the total and used to assess the liver function instead of the total ALP
10. Males or females age ≥18 years at the time of informed consent.
11. Subjects with known brain metastases will be eligible if they have completed the primary brain therapy (such as whole brain radiotherapy, stereotactic radiosurgery, or complete surgical resection) and if they have remained clinically stable, asymptomatic, and off of steroids for at least 28 days before starting study treatment.
12. All females must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin [β-hCG]) at the Screening Visit and the Baseline Visit. A pregnancy test needs to be performed within 72 hours of the first dose of study drug. Females of childbearing potential* must 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
    - 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.

13. Male subjects who are partners of women of childbearing potential must use a condom + spermicide and their female partners if of childbearing potential must use a highly effective method of contraception (see methods described in Inclusion Criterion #12) beginning at least 1 menstrual cycle prior to starting study drug(s), throughout the entire study period, and for 120 days after the last dose of study drug, unless the male subjects are totally sexually abstinent or have undergone a successful vasectomy with confirmed azoospermia or unless the female partners have been sterilized surgically or are otherwise proven sterile.
14. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.
15. Archival tumor tissue or a newly obtained biopsy must be available prior to the first dose of study drug for biomarker analysis. In the case archival tissue cannot be provided, patients with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the sponsor.
    Note: In case of submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut.

Exclusion Criteria

1. Prior anticancer treatment within 28 days (or 5 times the half-life time, whichever is shorter) or any investigational agent within 30 days prior to the first dose of study drugs. All acute toxicities related to prior treatments must be resolved to Grade ≤1.
2. Subjects must have recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.
3. Subjects having >1+ proteinuria on urinalysis will undergo 24-h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24-hour will be ineligible.
4. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib
5. New York Heart Association congestive heart failure of grade II or above, unstable angina, myocardial infarction within the past 6 months, or serious cardiac arrhythmia associated with significant cardiovascular impairment within the past 6 months
6. Prolongation of QTc interval to >480 msec
7. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug
8. Active infection (any infection requiring systemic treatment)
9. Subject is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C.
10. Serious nonhealing wound, ulcer, or bone fracture
11. Known intolerance to either of the study drugs (or any of the excipients)

12. History of organ allograft (subject has had an allogenic tissue/solid organ transplant)
13. Biologic response modifiers (eg, granulocyte colony-stimulating factor) within 4 weeks before study entry. Chronic erythropoietin therapy is permitted provided that no dose adjustments were made within 2 months before first dose of study treatment.
14. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial
15. Females who are pregnant or breastfeeding
16. Excluding the primary tumor leading to enrollment in this study, any other active malignancy (except for definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the bladder or cervix) within the past 24 months
17. Prior treatment with lenvatinib (no exceptions) or any PD-1, anti-PD-L1, or anti-PD-L2 agent, except:
    - the melanoma and NSCLC cohorts, where prior treatment with one anti-PD-1, anti-PD-L1, or anti-PD-L2 agent is allowed
    - the previously treated renal cell carcinoma subjects (as of Amendment 05) where prior treatment with one regimen containing an anti-PD-1/PD-L1 mAb is required.
18. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids (up to 7.5mg/d of prednisone or equivalent) may be approved after consultation with the sponsor.
19. No active autoimmune disease 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.
20. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
21. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

Study Treatments

Lenvatinib is provided as 4-mg and 10-mg capsules. Lenvatinib will be administered with water orally once a day (with or without food) in 21-day cycles at approximately the same time each day. Treatment cycles will be counted continuously regardless of dose interruptions. On D1 of each cycle, it will be administered approximately within 1 hour after completion of pembrolizumab administration.

Pembrolizumab may be provided as a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for IV infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab.

Alternatively, pembrolizumab may be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV 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 as a dose of 200 mg as a 30-minute IV infusion, Q3W (25 minutes to 40 minutes are acceptable). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

Study Treatment Dose Modification

Lenvatinib

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib-related toxicity will be in accordance with the dose reduction instructions shown in the tables below. For management of hypertension and proteinuria, refer to the main protocol text for instructions before consulting the table below, as appropriate. Any dose reduction below 4 mg/day must be discussed with the sponsor. Once the dose has been reduced, it cannot be increased at a later date. Dose reductions of lenvatinib in Phase 2 occur in succession starting at the RP2D dose identified in Phase 1b.

Lenvatinib Treatment-related Toxicity[a,b]	**During Therapy**	**Adjusted Dose[f]**
Grade 1, Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d] and Grade 3[g]		
First occurrence	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Grade 4[e,g]: Discontinue lenvatinib		

a. An interruption of lenvatinib treatment for more than 21 days (due to lenvatinib treatment-related toxicities) will require a discussion with the Sponsor before treatment can be resumed.

b. Excluding alopecia. Initiate optimal medical management for nausea, vomiting, hypothyroidism, hypertension, and/or diarrhea prior to any lenvatinib interruption or dose reduction. For treatment-related hypertension, refer to Management of Hypertension (Section 9.4.1.1.2) for dose modification guidelines.

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

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

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

f. Refer to table below for adjusted dose.

g. For asymptomatic Grade ≥3 elevations of amylase and lipase, the Sponsor`s Medical Monitor should be consulted to obtain permission to continue treatment.

Dose Reduction Recommendations for Lenvatinib Treatment-Related Toxicity

Initial Lenvatinib Dose (mg, QD)	**Adjusted Dose To Be Administered (mg, QD)**			
	Reduction 1	**Reduction 2**	**Reduction 3**	**Reduction 4**
24	20	14	10	8[a]
20	14	10	8	4[a]

14	10	8	4[a]	

QD = once a day

a: Consult the sponsor for further dose reduction recommendations.

General guidelines for holding periods of lenvatinib due to procedures:

For minor procedures, lenvatinib should be stopped 2 days before the procedure and restarted 2 days after, once there is evidence of adequate healing and no risk of bleeding. Needle biopsies (fine needle aspirations and core needle aspiration) are usually considered minor procedures.

For major procedures, lenvatinib should be stopped at least 1 week (5 half-lives) before the procedure and then restarted once there is clear wound healing and no risk of bleeding, but at least 2 weeks after the procedure. It is up to the investigator to determine if it is a major or minor procedure. Usually a major procedure implies general anesthesia.

Pembrolizumab

Pembrolizumab dose interruption for subjects who experience pembrolizumab-related toxicity will be in accordance with the table below.

Adverse events (AEs) (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per the table below. See Protocol for supportive care guidelines, including use of corticosteroids.

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

Immune-related Adverse Event	Toxicity Grade (CTCAE v4.0)	Action with Pembrolizumab	Corticosteroids and/or Other Therapies	Monitoring and Follow-up
General instructions: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. **If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.**				
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold		

	Recurrent Grade 3 or Grade 4	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants 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). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants 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.
AST or ALT elevation or Increased Bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper. Administer corticosteroids (initial dose of 1 to 2 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[a]	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants 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, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care.	Monitor for signs and symptoms of thyroid disorders.
	Grade 2	Withhold		

Nephritis: grading according to increased creatinine or acute kidney injury.	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (prednisone 1to 2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function.
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 2, 3 or 4	Permanently discontinue		
All other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3	Withhold or discontinue based on event[b].		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s) = adverse event(s), ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI = gastrointestinal, IO=immuno-oncology; irAE = immune-related adverse event, IV = intravenous; SJS=Stevens-Johnson Syndrome; T1DM = Type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

Duration of Treatment

Study duration for each subject is estimated to be:

- **Pretreatment Phase:** 4 weeks
- **Treatment Phase:**
  - **Phase 1b:** 3 weeks (1 cycle)
  - **Phase 2:** 24 weeks (8 cycles)
- **Phase 1b and 2 Extension Phase:** Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, subject choice, withdrawal of consent, completion of 35 treatments (approximately 2 years) with pembrolizumab, lost to follow up or discontinuation of this study by the sponsor. Subjects who discontinued pembrolizumab for any reason and are still receiving lenvatinib study drug, will be transitioned to commercial lenvatinib if local country regulations permit.

Efficacy Assessments:

Tumor assessments will be performed by the investigators based on both irRECIST and modified RECIST 1.1. Treatment decisions by the investigator will be based on irRECIST. All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The Scans from Phase 1b must be accessible in the event of a sponsor request to submit them for central review. For Phase 2, images acquired for tumor assessments will be sent to an imaging core laboratory (ICL)for archiving and potential independent analysis. As of Amendment 3, tumor assessment scans for the EC subjects will be assessed by IIR. As of Amendment 5, tumor assessment scans for the renal cell carcinoma subjects will also be assessed by IIR. As of Amendment 08, for subjects enrolled in the RCC cohort who were previously treated with anti-PD-1/PD-L1 mAb, available pre-Baseline scans that demonstrate previous progression, will be collected by sites and sent to an ICL designated by the sponsor for quality assessment and archival, and potential future independent review.

As of Amendment 08, scans acquired after data cutoff for final efficacy analysis, in any cohort, will no longer be sent to the imaging core lab. As of Amendment 09, pre-baseline scans for RCC subjects are not required.

Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks (during the sixth week; counting from C1D1) until Week 24, then every 9 weeks during treatment cycles in both the Treatment Phase and the Extension Phase. As of Amendment 09, tumor assessments will continue during the Extension Phase as per local standard of care but not less frequent than every 6 months. Tumor assessments will not be collected during the Follow-Up period of the Extension Phase. Magnetic resonance imaging /MRI scans of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1 Day 1), at all tumor assessment time points, and as indicated clinically and as per local standard of care. Color photographs containing a millimeter scale must be taken of all skin lesions being used as target lesions. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable. Subjects with squamous cell carcinoma of the head and neck must also have head and neck scans performed.

Magnetic resonance imaging may be used instead of CT for head, neck, abdomen, and pelvis; however, the chest must be assessed using CT. Chest disease may not be followed using chest x-ray.

A brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at Screening to assess potential central nervous system (CNS) disease and/or metastases. For subjects with previously treated eligible brain metastases, a brain scan must be performed at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm immune-related complete response (irCR) within 1 week of response confirmation, or if clinically indicated.

The tumor assessment schedule should not be affected by interruptions in study treatment.

Subjects going Off-Tx without disease progression will also undergo tumor assessments per the Schedule of Procedures/Assessments until disease progression is documented or another anticancer therapy is initiated.

The same method of assessment must be used at all-time points as was used at Screening. Throughout the study it is critical that the same imaging methodology be applied and contrast be consistently provided unless IV contrast becomes medically contraindicated during the course of treatment or the dose of contrast needs to be adjusted based on the subject's health status.

Bone scans will be performed at Screening, every 24 weeks, or sooner if clinically indicated, and at confirmation of irCR (except for subjects with squamous cell carcinoma of the head and neck). Lesions identified on bone scans must be verified and followed with correlative cross-sectional imaging.

In order for immune-related stable disease (irSD) to be considered the best overall response, it must occur ≥5 weeks following the first dose of study drug.

The first radiological assessment of tumor response status will be performed at Week 6 (±1 week), unless there is clinical indication warranting earlier radiologic imaging. If imaging at Week 6 shows irSD, treatment will be continued and tumor assessments will be conducted at the next regularly scheduled imaging time point, ie, at Week 12 (±1 week). Responses (irPR [PR] or irCR) should be confirmed no less than 4 weeks after the initial response, but generally at the next scheduled tumor assessment time point.

If the time point tumor assessment is PD, treatment should continue and tumor assessments be repeated at least 4 weeks later, but generally at the next scheduled tumor assessment time point in order to confirm immune-related progression disease (irPD). If repeat imaging shows a reduction in the tumor burden compared to the initial tumor assessment demonstrating PD, treatment may be continued as per treatment schedule. If repeat imaging confirms irPD, subjects will be discontinued from study treatment. In determining the tumor time point response, investigators should consider all target lesions as well as nontarget lesions and new lesions. The decision to continue study treatment after the first evidence of PD is at the investigator's discretion based on the clinical status of the subject.

Subjects may continue receiving study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG PS
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

If irPD is confirmed and the subject is experiencing extraordinary clinical benefit, the site must contact the sponsor to discuss continuing treatment.

Tumor assessments per modified RECIST 1.1 will follow Eisenhauer, et al. (2009); however, up to 10 target lesions, up to 5 per organ, may be selected (as opposed to a maximum of 5 target lesions, up to 2 per organ).

Pharmacokinetic:

Plasma concentrations of lenvatinib will be measured.

Dose-normalized PK profile for lenvatinib in combination with pembrolizumab from this study will be compared graphically to that from patients with different tumor types from completed studies of those receiving lenvatinib monotherapy.

Pharmacodynamic/Pharmacogenomic:

Blood and Tissue Biomarkers: Blood samples for the development of exploratory predictive biomarkers will be collected prior to the first dose of study drug, on Cycle 1 Day 15, and on D1 of all subsequent cycles during Treatment Phase, and at the Off-Tx assessment. Subjects will be required to provide an archival tumor tissue sample and/or a fresh biopsy of tumor before treatment for biomarker analyses (patients with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the sponsor). For subjects in the NSCLC

cohort every effort is to be made to obtain a fresh biopsy of tumor at the beginning of Cycle 2 (optional for other cohorts on study) if they have recovered adequately from the biopsy taken prior to starting therapy and to provide the acquired tissue for these biomarker analyses. Biomarker discovery and/or validation will be performed to identify blood or tumor biomarkers that may be useful to predict subject response to lenvatinib and/or pembrolizumab, as determined by evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Blood samples from subjects receiving lenvatinib and pembrolizumab may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods or new technology. In addition, biomarkers identified in other lenvatinib clinical studies may also be assessed in the biomarker 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.

Archived, formalin-fixed paraffin-embedded (FFPE) tissue or a newly obtained biopsy will be collected from all subjects for potential assessment of mutations and other genetic alterations and/or proteins including PD-1/PD-L1 status and other relevant biomarkers (eg, tumor infiltrating lymphocytes, T-cell repertoire, ribonucleic acid [RNA] signature profiles) which may be important in the development and progression of cancer as well as for potential use in diagnostic development. Appropriate technology/methodologies will be used based on the amount of tumor tissue available.

For all tumor types except NSCLS, optional fresh paired tumor biopsies will be collected from consented subjects to examine markers including markers of target engagement, relevant pharmacodynamic biomarkers, and potential markers of response. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin, peripheral lymph nodes, liver metastases that can be readily accessed using CT guidance). Subjects should have the biopsy before administration of the first dose of study drug and at a time point 3-6 weeks after the first dose (if they have recovered adequately from the biopsy taken prior to starting therapy). For NSCLC, every effort is to be made to obtain a fresh tumor biopsy; subjects will have fresh tumor biopsies collected from consented subjects before administration of the first dose of study drug and at a time point 3-6 weeks after the first dose (if they have recovered adequately from the biopsy taken prior to starting therapy).

A blood sample for peripheral blood mononuclear cells and plasma isolation will be collected from enrolled subjects. Cell free nucleic acid isolated from plasma samples may be used to obtain circulating tumor DNA (ctDNA) and explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment.

In Phase 2, as of Amendment 4, a blood sample for nucleic acid analysis will be collected for potential assessment of gene expression profiling. In Phase 2, as of Amendment 3, a blood sample will be collected for potential pharmacodynamics and pharmacogenomics analysis. Variation in lenvatinib exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor, for potential microsatellite instability analysis, and for potential immune response monitoring.

As of Amendment 06, available known mutation status including mismatch repair (MMR) or microsatellite instability (MSI) status will be collected on the case report form.

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

15 years to assist in any research scientific questions related to lenvatinib/pembrolizumab, cancer, and/or for potential diagnostic development.

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

Safety:

Safety assessments will consist of monitoring and recording all AEs and serious adverse events, using Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03; regular laboratory evaluation for hematology, blood chemistry, and urine values; regular performance of physical examinations (including oral examinations), periodic measurement of vital signs, and ECGs.

Bioanalytical Methods

Lenvatinib will be quantified using validated HPLC-tandem mass spectroscopy method.

Statistical Methods

Study Endpoints

ORR$_{(Week\ 24)}$ is defined as the proportion of subjects who have best overall response (BOR) of irCR$_{(Week\ 24)}$ or irPR$_{(Week\ 24)}$ as of the Week 24 tumor assessment time point.

ORR is defined as the proportion of subjects who have BOR of irCR or irPR at the time of data cutoff.

PFS is defined as the time from the first study dose date to the date of first documentation of confirmed disease progression or death (whichever occurs first).

OS is measured from the start date of the treatment period until date of death from any cause. Subjects who are lost to follow-up and the subjects who are alive at the date of data cutoff will be censored at the date the subject was last known alive.

DCR is defined as the proportion of subjects who have BOR of irCR or irPR or irSD (duration of irSD ≥5 weeks).

CBR is defined as the proportion of subjects who have BOR of irCR or irPR or durable irSD (duration of irSD ≥23 weeks).

DOR is defined as the duration of irCR or irPR.

Durable SD rate is defined as the proportion of subjects whose BOR is irSD and the duration of irSD is ≥23weeks.

As exploratory analyses, tumor response endpoints will be evaluated for the subjects in the endometrial and renal cell carcinoma analysis sets using the IIR assessments.

Analysis Sets:

Safety Analysis Set will include all subjects who received any amount of study drug. This will be the analysis set for all safety evaluations.

MTD Analysis Set will include all subjects who completed Cycle 1 of treatment of Phase 1b or discontinued early due to DLT. This will be the analysis set to determine MTD.

Full Analysis Set (Intent-to-Treat [ITT] Analysis Set) will include all subjects who entered the study treatment period.

PK Analysis Set: All the subjects who have received at least 1 dose of lenvatinib and have evaluable concentration data.

Pharmacodynamic Analysis Set will include all subjects who have received at least 1 dose of study drug (lenvatinib or pembrolizumab) and have evaluable pharmacodynamic data.

Endometrial Carcinoma Analysis Set: will include all EC subjects from Phase 1b and Phase 2.

Renal Cell Carcinoma Analysis Set will include all renal cell carcinoma subjects from Phase 1b and Phase 2.

Non-Small Cell Lung Cancer Analysis Set will include all NSCLC subjects from Phase 1b and Phase 2.

Melanoma Analysis Set will include all melanoma subjects from Phase 1b and Phase 2.

Efficacy Analyses

Selected efficacy analyses may be performed if needed for subjects with the combination of lenvatinib and pembrolizumab as the first line treatment versus other subjects with prior systemic therapies. For the renal cell carcinoma cohort, efficacy subgroup analyses may be presented for treatment naïve subjects, subjects who were previously treated with an anti-PD-1/PD-L1 therapy, and subjects who were previously treated without an anti-PD-1/PD-L1 therapy.

Analysis of Primary Endpoint for Phase 1b:

The primary objective of Phase 1b is to determine the DLTs, MTD, and to establish the RP2D. The efficacy endpoints in Phase 1b will be summarized and listed by dose level based on the Safety Analysis Set. No statistical comparison will be performed.

Analysis of Efficacy Endpoints for Phase 2:

Efficacy analyses will primarily be based on the Full Analysis Set. Efficacy (eg, $ORR_{(Week\ 24)}$, ORR, BOR during the Treatment and Extension Phases, PFS, DCR, durable SD, CBR) will be assessed by irRECIST and modified RECIST 1.1. The efficacy endpoints will be summarized and listed by cohort. No statistical comparison will be performed.

Analysis of Primary Efficacy Endpoint for Phase 2:

The primary efficacy endpoint in Phase 2 is ORR as of Week 24 ($ORR_{(Week\ 24)}$) based on irRECIST based on the Full Analyses Set. Estimated $ORR_{(Week\ 24)}$ and the exact 95% confidence intervals (CI) using the method of Clopper–Pearson will be presented. The primary efficacy analysis will be performed when all subjects in the same cohort have completed 8 cycles of treatment, discontinued due to disease progression, developed unacceptable toxicity, withdrew consent, or the study is terminated by the Sponsor.

Analysis of Secondary Efficacy Endpoints for Phase 2:

The secondary efficacy endpoint will be OS, PFS, DCR, CBR, DOR, and durable SD (SD ≥23 weeks) by irRECIST as appropriate.

Median time to PFS and 95% CI will be provided for the data from this study by cohort as well as historical control data if available, and PFS will be analyzed using Kaplan–Meier (KM) product-limit estimates along with KM plots. Three-month, 6-month, 9-month and 1-year PFS rates will be estimated from KM and corresponding 95% CI will be calculated.

Median survival time and the 95% CI, the survival rates at 12, 18 and 24 months will be calculated using KM product-limit estimates for each cohort and presented with 2-sided 95% CIs. KM plots for OS will be provided.

Disease Control Rate, CBR, and durable SD rate will be provided with exact 95% CI using the method of Clopper and Pearson.

Analysis of Exploratory Efficacy Endpoints:

The tumor response endpoints will be explored based on modified RECIST 1.1 assessments, and will be summarized and listed by cohort. No statistical comparison will be performed between irRECIST and modified RECIST 1.1 results.

The tumor response endpoints will also be evaluated for the subjects in the endometrial and renal cell carcinoma analysis sets using IIR assessment using irRECIST, modified RECIST 1.1 and RECIST 1.1 as exploratory analyses. A concordance analysis will be performed comparing IIR and investigator assessments.

Pharmacokinetic and/or Pharmacodynamic Analyses

Pharmacokinetic:

To assess any drug–drug interaction between lenvatinib and pembrolizumab, the dose-normalized PK profile for lenvatinib in combination with pembrolizumab from this study will be compared graphically to that from patients with different tumor types from completed studies of those receiving lenvatinib monotherapy.

Pharmacodynamic:

The effect of lenvatinib-pembrolizumab combination therapy on soluble, tissue, genetic and/or imaging biomarkers will be summarized using descriptive statistics using the pharmacodynamic analysis set.

Safety Analyses:

Safety analyses will be performed on the Safety Set. 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 (SD), median, and range (minimum and maximum) unless otherwise specified. Laboratory test results will be summarized using 3 categories, hematology, liver and renal, and other clinical chemistry. Hematology and clinical chemistry parameters that are graded by CTCAE v 4.03 will be summarized by CTCAE grade. Shifts from baseline to the worst CTCAE grade will be tabulated.

Selected safety analyses may be performed if needed for subjects with the combination of lenvatinib and pembrolizumab as the first line treatment versus other subjects with prior systemic therapies. For the renal cell carcinoma cohort, safety subgroup analyses may be presented for treatment naïve subjects, subjects who were previously treated with an anti-PD-1/PD-L1 therapy, and subjects who were previously treated without an anti-PD-1/PD-L1 therapy.

Sample Size Rationale

Phase 1b: A sample size of 10 to 30 subjects will be enrolled to assess MTD. This is not based on statistical power considerations.

Phase 2: A sample size of 10 evaluable subjects will be enrolled per cohort, with the possibility of expansion to 20 evaluable subjects per cohort, depending on the evaluation by the sponsor and investigators of the efficacy and safety results observed with the initial 10 evaluable subjects in each cohort.

As of Amendment 3, the EC cohort may be further expanded to approximately 120 evaluable subjects. For this expansion decision, 2 interim analyses will take place when 21 and 60 subjects have sufficient follow-up to be evaluated for response. The decision to expand enrollment will be based on the results of 2 interim analyses, which will spend $\beta = 0.012$ and $\beta = 0.024$ at the first and second interim analyses, respectively. Based on an assumption of H_0: 16% ORR and H_1: 34% ORR, at 2-sided $\alpha = 0.02$, this design will give 97% statistical power with 120 subjects. At the first interim analysis (N = 21), if there are more than 3 responses, then approximately 40 additional subjects will be enrolled. At the second interim analysis (N = 60), if there are more than 12 responses, approximately 60 additional subjects will be enrolled. If there are 12 or fewer responses, the sponsor may decide whether to expand enrollment based on clinical outcome, eg,

ORR and DOR. If the expansion beyond 60 subjects does not happen, this design for the EC cohort has approximately 86% power at 2-sided $\alpha = 0.02$.

As of Amendment 7, the renal cell carcinoma cohort may be further expanded to approximately 145 total evaluable subjects to allow for approximately 100 evaluable subjects who have received 1 or 2 prior therapies that included an anti-PD-1/PD-L1 mAb. The decision to expand enrollment will be based on the results of 2 interim analyses. The first interim analysis will take place when 22 subjects (11 treatment naïve and 11 previously treated without an anti-PD-1/PD-L1 mAb) have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 22), if there are more than 5 responses, then approximately 45 additional subjects will be enrolled. It is anticipated that the additional 45 subjects will consist of approximately 12 treatment naïve subjects enrolled under Amendment 5 and approximately 33 previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 mAb. The second interim analysis will include these 45 additional subjects and the 11 treatment naïve subjects included in the first interim analysis and will take place when these 56 subjects have sufficient follow-up to be evaluated for response. At the second interim analysis, whether the previously treated renal cell carcinoma subset will be further expanded will be decided based on clinical review of both efficacy and safety data.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

^{18}F-NaF-PET	18F Sodium Fluoride (NaF) positron emission tomography
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
β	beta
BMI	body mass index
BOR	best overall response
BP	blood pressure
C#/D#	Cycle#/Day#
CA	Competent Authority
CBR	clinical benefit rate
CCG	CRF completion guideline
cf-nucleic acid	cell free nucleic acid
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	clinical laboratory improvement amendments
C_{max}	maximum concentration
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
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
CYP	cytochrome P450
D1	Day 1
D15	Day 15

DCR	disease control rate
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSDR	durable stable disease rate
EC	endometrial carcinoma
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FDA	United States Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HNSCC	squamous cell carcinoma of head and neck
ICF	informed consent form
ICH	International Conference on Harmonisation
ICL	imaging core laboratory
IEC	Independent Ethics Committee
IIR	independent imaging review
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irCR	immune-related complete response
irPD	immune-related progression disease
irPR	immune-related partial response
IRR	independent radiologic review
irRECIST	immune-related RECIST
irSD	immune-related stable disease
ITT	intent to treat
IUD	intrauterine device
IUS	intrauterine system
IV	Intravenous
KIT	a stem cell factor receptor
KM	Kaplan–Meier

KPS	Karnofsky performance status
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDi	longest diameter
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMR	mismatch repair
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
N	number
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
Off-Tx	Off Treatment
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1 (or 2)	PD-1 ligand 1 (or 2)
PET	Positron emission tomography
PFS	progression-free survival
PG	pharmacogenomics
P-gp	P-glycoprotein
PI	principal investigator
PK	Pharmacokinetics
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PT	preferred term
pTNM	pathological tumor-node-metastasis
Q3W	every 3 weeks

QD	once a day
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	calculated QT
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDi	short axis
SOC	system organ class
SOD	sum of diameters
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TKI	tyrosine kinase inhibitor
UC	urothelial carcinoma
TAM	tumor- associated macrophage
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
T_{max}	time to maximum concentration
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
$VEGFR_{1-3}$	vascular endothelial growth factor receptor 1, 2, 3

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 [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in Clinical Research Associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

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

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The definition for end of the study for each cohort is the time of data cutoff for the final analysis or the time of last subject/last treatment, whichever occurs later. It is estimated that the study duration will be 24 months. 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 (SOPs) 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 Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.
- 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 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.

For assessments with pharmacodynamic, pharmacogenomic (PG), or other biomarker assessments, subjects will be asked to sign an additional consent for these assessments (see Section 9.5.1.4.2).

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 25 investigational site(s) in the US and EU.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and, if applicable, of the contract research organization(s) (CRO(s)) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

Study E7080-A001-111, which will be conducted in patients, has 2 goals. One is to determine the maximum tolerated dose (MTD) of the combination of a programmed cell death protein 1 (PD-1) inhibitor (pembrolizumab) with the tyrosine kinase inhibitor (TKI) lenvatinib. The second is to assess the safety and efficacy of the combination in selected tumors.

7.1 Indication

7.1.1 PD-1 Inhibitors and Pembrolizumab

Antitumor immunity is often ineffective due to the tight regulation associated with the maintenance of immune homeostasis (Stagg, 2013). Recent studies have shown that cancer cells, as well as stromal cells and immune cells in the cancer microenvironment can upregulate expression of the B7 family of inhibitory molecules. These are peripheral membrane proteins found on activated antigen presenting cells (Coico, et al., 2003).

Compelling evidence indicates that B7 proteins can suppress T-cell responses (Chen, 2004; Sharpe and Freeman, 2002) aiding tumor immune evasion. These negative signals are largely provided by two members of the B7-family. One of these is PD-1, also known as B7-H1. PD-1 limits T cell effector functions within tissues by negatively regulating antitumor CD8 T cell responses. By upregulating ligands for PD-1, tumor cells block antitumor immune responses in the tumor microenvironment. Indeed, expression of the PD-1 ligand (PD-L1) has been shown to be associated with poor prognosis in melanoma and hepatocellular carcinoma (Topalian, et al., 2012; Gadiot, et al., 2011; Gao, et al., 2009).

Clinically, blockade of PD-1 or PD-L1, using monoclonal antibodies (mAbs), has demonstrated substantial clinical activity in patients with metastatic melanoma, RCC, non-small cell lung cancer (NSCLC), bladder, head and neck cancers, and other tumors (Philips and Atkins, 2015; Robert, et al., 2014; Hamid and Carvajal, 2013; Brahmer, et al., 2012).

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with NSCLC, head and neck squamous cell carcinoma, urothelial carcinoma (UC), gastric cancer, triple negative breast cancer and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the Investigator's Brochure.

7.1.2 Lenvatinib

Lenvatinib is an oral, multi–TKI active against ret proto-oncogene, vascular endothelial growth factor receptor (VEGFR)1–3, FGFR1–3, a stem cell factor receptor (KIT), and platelet-derived growth factor receptor α (Yamamoto, et al., 2014; Tohyama, et al., 2014; Okamoto, et al., 2013; Matsui, et al., 2008a; Matsui, et al., 2008b). It is approved in the US for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, and in combination with everolimus for patients with advanced renal cell carcinoma following 1 prior antiangiogenic therapy. In the EU, lenvatinib is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine, and in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma following 1 prior vascular endothelial growth factor-targeted therapy. As outlined below, data from Phase 2 clinical studies showed lenvatinib has antitumor activity in multiple other tumors.

In patients with locally advanced or metastatic nonsquamous NSCLC, treated with lenvatinib 24 mg once daily + best supportive care, lenvatinib was found to be active with longer survival in these subjects who had had 2 or more lines of prior treatment. Overall survival (OS) was the primary objective of this study.

In a study (E7080-G000-204) to evaluate the antitumor activity of lenvatinib 24 mg orally once daily in female subjects with surgically unresectable endometrial carcinoma (EC) who have disease progression following 1 prior platinum-based, systemic chemotherapy regimen, the ORR (complete response [CR] + partial response [PR]) was 14.3% based on the assessments by independent radiologic review (IRR), the primary endpoint of the study. The

ORR based on investigator assessments was 21.1%, indicating that lenvatinib is active as a second-line treatment in subjects with advanced EC.

A study was conducted to determine the activity of lenvatinib in previously treated subjects with unresectable Stage III or Stage IV melanoma (E7080-G000-206). The primary endpoint of the study was ORR, based on IRR assessment for the intent-to-treat (ITT) population. The ORR was 8.6% in subjects with melanoma not harboring the V600E BRAF mutation and 9.0% in subjects with melanoma harboring the activating BRAF mutations (mainly the V600E mutation). All were PRs.

7.2 Study Rationale

The effect of combining lenvatinib with PD-1/L1 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) (Data on File). Combination treatment with lenvatinib and PD-1/L1 mAb showed significant and superior antitumor effects compared with either compound alone. Tumor-associated macrophage (TAM) cells express PD-L1 at a higher level than cancer cells in the CT26 syngeneic model, and lenvatinib significantly decreased the TAM population (Data on File). Because TAM cells produced interleukin 10 (IL-10) and transforming growth factor, beta 1 (TGFβ) (Noy and Pollard, 2014), lenvatinib might increase antitumor immunity in the CT26 model and up-regulate the effect of the PD-1 signal inhibitors.

For the assessment of MTD, the lenvatinib doses selected are 24 mg, 20 mg, and 14 mg once a day (QD) all in conjunction with 200 mg pembrolizumab every 3 weeks (Q3W). 24 mg is the recommended dose for locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (LENVIMA Package Insert/SmPC). 20 mg and 14 mg are the first and second doses in lenvatinib's dose reduction scheme for all tumors (except hepatocellular carcinoma) for which data are available.

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda® development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W)
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg

Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a physiologically-based PK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed dose was selected for evaluation across all pembrolizumab protocols.

No dose reduction is allowed for pembrolizumab in this study.

8 STUDY OBJECTIVES

8.1 Primary Objectives

- Phase 1b – Determination and confirmation of the MTD:
  To determine and confirm the MTD for lenvatinib in combination with 200 mg (IV, Q3W) pembrolizumab in subjects with selected solid tumors.

- Phase 2 – Expansion In Selected Tumor Types (Expansion):
  To evaluate ORR as of Week 24 ($ORR_{(Week\ 24)}$: CR + partial response [$CR_{(Week\ 24)}$ + $PR_{(Week\ 24)}$]) of lenvatinib in combination with pembrolizumab in each of the cohorts using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).

8.2 Secondary Objectives (for both Phase 1b and 2)

To assess:

- Tolerability and safety profile of lenvatinib in combination with pembrolizumab
- ORR by irRECIST of lenvatinib in combination with pembrolizumab in subjects with solid tumors
- Progression-free survival (PFS) by irRECIST
- OS
- Duration of response (DOR) by irRECIST
- Disease control rate (DCR: CR + PR + stable disease [SD]) by irRECIST
- Durable stable disease rate (DSDR [SD ≥23 weeks]) by irRECIST
- Clinical benefit rate (CBR: CR, PR + durable SD) by irRECIST
- PK profiles of lenvatinib during combination treatment.

8.3 Exploratory Objectives

- To explore tumor response (eg, PR, CR, SD, PD) based on modified RECIST 1.1 assessments
- To explore tumor response in subjects with EC and renal cell carcinoma based on independent imaging review (IIR) using irRECIST, modified RECIST 1.1, and RECIST v1.1.
- To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of lenvatinib in combination with pembrolizumab:
  a. To evaluate the relationship between PD-L1 expression levels and other relevant biomarkers (eg, tumor infiltrating lymphocytes, T-cell repertoire, ribonucleic acid [RNA] signature profiles) in tumor samples and anti-tumor activity of lenvatinib in combination with pembrolizumab.
  b. To evaluate differences in tumor tissue characteristics in biopsies taken post treatment with lenvatinib in combination with pembrolizumab versus baseline.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

Overall Design:

E7080-A001-111 is a multicenter, open-label study in subjects with selected solid tumors. All subjects in the study will receive lenvatinib and pembrolizumab while participating in the study. The study has 2 phases, Phase 1b and Phase 2. In Phase 1b, 10 to 30 evaluable subjects will be enrolled in 1 to 3 dose levels to determine the recommended Phase 2 dose (RP2D). In Phase 2, a sample size of 10 evaluable subjects will be enrolled per cohort, with the possibility of expansion to 20 evaluable subjects per cohort, depending on the evaluation by the sponsor and investigators on the efficacy and safety results observed with the initial 10 evaluable subjects in each cohort.

The EC cohort may be further expanded to approximately 120 subjects. The decision to expand enrollment will be based on the results of 2 interim analyses that will take place when 21 and 60 subjects have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 21), if there are more than 3 responses, then approximately 40 additional subjects will be enrolled. At the second interim analysis (N = 60), if there are more than 12 responses, approximately 60 additional subjects will be enrolled. If there are 12 or fewer responses, the sponsor may decide whether to expand enrollment based on clinical outcome, eg, ORR and DOR.

The renal cell carcinoma cohort may be further expanded to approximately 145 total renal cell carcinoma (RCC) subjects to allow for approximately 100 evaluable subjects who have received 1 or 2 prior therapies that included an anti-programmed cell death protein 1 (PD)-1/PD-L1 mAb. The decision to expand enrollment will be based on the results of 2 interim analyses. The first interim analysis will take place when 22 subjects (11 treatment naïve and 11 previously treated without an anti-PD-1/PD-L1 mAb) have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 22), if there are more than 5 responses, then approximately 45 additional subjects will be enrolled. It is anticipated that the additional 45 subjects will consist of approximately 12 treatment naïve subjects enrolled under Amendment 05 and approximately 33 previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 mAb, administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies, and as of Amendment 07, the regimen with an anti-PD-1/PD-L1 mAb must be the most recent therapy. PD-1 treatment progression is defined by meeting all of the following criteria:

a) Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb
b) Has demonstrated disease progression after PD-1/PD-L1 as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The initial evidence of disease progression (PD) is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented PD

c) Progressive disease (PD) has been documented within 12 weeks from last dose of anti-PD-1/PD-L1 mAb (refractory disease) or ≥12 weeks from last dose of anti-PD-1/PD-L1 mAb (late relapses)

The second interim analysis will include these 45 additional subjects and the 11 treatment naïve subjects included in the first interim analysis, and will take place when these 56 subjects have sufficient follow-up to be evaluated for response. At the second interim analysis, whether the previously treated renal cell carcinoma subset will be further expanded will be decided based on clinical review of both efficacy and safety data.

For subjects in Phase 1b and Phase 2, toxicity will be managed by treatment interruption, dose reduction, and/or treatment discontinuation in accordance with the dose modification instructions outlined in Table 2 and Table 4 below. Treatment will continue until disease progression, development of unacceptable toxicity, subject choice, withdrawal of consent, completion of 35 treatments (approximately 2 years) with pembrolizumab, lost to follow up or discontinuation of this study by the sponsor. Patients can receive up to 35 treatments (approximately 2 years) with pembrolizumab. Subjects who discontinue pembrolizumab after 35 treatments may continue treatment with lenvatinib alone unless any other criteria above apply. Subjects who discontinued pembrolizumab for any reason and are still receiving lenvatinib study drug, will be transitioned to commercial lenvatinib if local country regulations permit.

Phase 1b - MTD:

Dosing will begin at the full dose of both drugs due to the well-established safety profiles of lenvatinib and pembrolizumab, the nonoverlapping mechanisms of action, and the desire to treat patients at doses shown to be effective in previous studies. Lower dose levels of lenvatinib will be explored as necessary depending on observed toxicity.

Phase 1b will determine and confirm the MTD of lenvatinib in combination with pembrolizumab. Subjects in Phase 1b will have one of the following tumors: non-small cell lung cancer, renal cell carcinoma, EC, UC, squamous cell carcinoma of head and neck (HNSCC), or melanoma. The dose of 1 of the 2 study drugs, pembrolizumab, will not change during the MTD phase, while the second study drug, lenvatinib, will start at 24 mg and then be reduced, if necessary, to either 20 mg or 14 mg. Phase 1b is illustrated in Figure 1.

Phase 1b will begin at Dose Level 1: lenvatinib 24mg/day orally and pembrolizumab 200 mg every 3 weeks, IV will be administered to subjects with selected solid tumors on a 21-day treatment cycle. Two dose de-escalation steps are included: Dose Level 2 (lenvatinib 20 mg/day orally + pembrolizumab 200 mg Q3W, IV) and Dose Level 3 (lenvatinib 14 mg/day orally + pembrolizumab 200 mg Q3W, IV). For determination of MTD, only dose limiting toxicities (DLTs), as defined in Table 1, during the first cycle of treatment, will be assessed. The determination of the DLT will be made jointly by the sponsor and investigators after safety data from each dose level have been reviewed.

If 0 of 3 subjects in a given dose level cohort experiences a DLT, then 7 more subjects will be enrolled into that dose level to confirm the MTD. If 1 of 3 subjects has a DLT, then 3

more subjects will be enrolled into that dose level for a total of 6 subjects. If only 1 of these 6 subjects has a DLT, then 4 more subjects will be enrolled into that dose level to confirm the MTD.

As shown in Figure 1, if 2 or more subjects at a dose level experience a DLT, then, following consultation with the PIs the study will proceed with enrollment in the next defined lower dose (Dose Level 2 or 3), with dose reduction of lenvatinib to 20 or 14 mg QD, respectively, in combination with 200 mg pembrolizumab Q3W.

For confirming the MTD, DLTs and intolerable toxicities (that cannot be managed with dose interruption and/or reduction) during the first cycle of treatment for the 10 evaluable subjects at that dose level will be assessed. The MTD will be confirmed if no more than 3 subjects experience DLTs during the first 3 weeks (Cycle 1) of treatment. If the MTD is not confirmed at a dose level, then enrollment will proceed to the next lower dose level. The sponsor and investigators will review all subjects' safety and clinical data to jointly determine the RP2D of the combination of lenvatinib with pembrolizumab.

If 2 or more subjects have a DLT in Dose Level 3, enrollment in the study will stop.

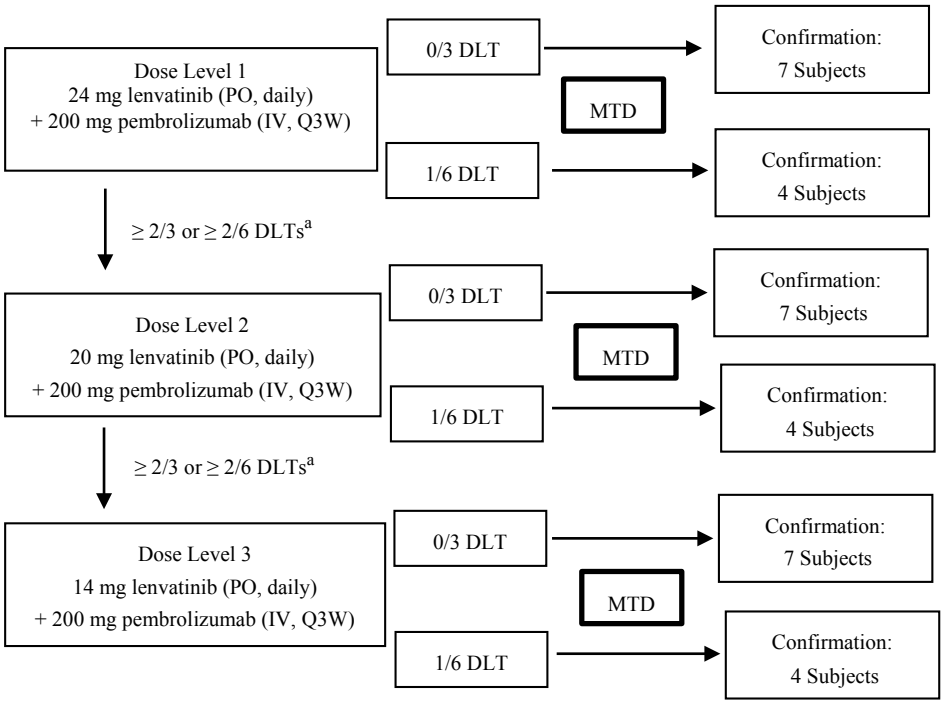


Figure 1 Phase 1b – Determination and Confirmation of the Maximum Tolerated Dose

DLT = dose limiting toxicity, IV = intravenous, MTD = maximum tolerated dose, PO = orally, Q3W – every 3 weeks

a: where DLTs are considered lenvatinib related.

A DLT is defined as any of the following:

- Any of the hematological or nonhematological toxicities noted in Table 1 considered to be at least possibly related to lenvatinib and/or pembrolizumab occurring during Cycle 1.

- Failure to administer ≥75% of the planned dosage of lenvatinib as a result of treatment-related toxicity during Cycle 1.

- Subjects who discontinue treatment due to treatment-related toxicity.

- Greater than 2 week delay in starting Cycle 2 because of a treatment-related toxicity, even if the toxicity does not meet DLT criteria.

Table 1 Dose-Limiting Toxicities

Toxicity Category	Toxicity CTCAE Grade
Hematologic	• Grade 4 neutropenia for ≥7 days • Grade 3 or Grade 4 febrile neutropenia[a] • Thrombocytopenia <25,000/mm^3 associated with bleeding and/or which requires platelet transfusion

Other nonhematologic toxicity	• Any other Grade 4 or a Grade 5 toxicity
	• Grade 3 toxicities lasting >3 days excluding:
	  • Nausea, vomiting, and diarrhea controlled by medical intervention within 72 hours.
	  • Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab.
	• Grade 3 hypertension not able to be controlled by medication
	• Grade 3 or above gastrointestinal perforation
	• Grade 3 or above wound dehiscence requiring medical or surgical intervention
	• Any grade thromboembolic event

	Any Grade 3 nonhematologic laboratory value if: • Medical intervention is required to treat the subject, or • The abnormality leads to hospitalization

ANC = absolute neutrophil count, CTCAE = Common Terminology Criteria for Adverse Events v4.03.
a. Febrile neutropenia Grade 3 or Grade 4:
Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour.
Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour, with life-threatening consequences and urgent intervention indicated

Only toxicities with a clear alternative explanation (eg, due to disease progression) or transient (≤72 hours), abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination, can be deemed a non-DLT.

All subjects enrolled in Phase 1b will be assessed for DLTs during the DLT assessment window of Cycle 1 (Treatment Phase). Subjects who discontinue study treatment prior to completing the Treatment Phase for any reason other than DLT will be replaced. Once they complete the Treatment Phase, each subject still receiving study treatment will transition into the Extension Phase. Tumor assessments will continue during the Extension Phase. As of

Amendment 09, tumor assessments will continue during the Extension Phase as per the local standard of care but not less frequent than every 6 months. Tumor assessments will not be collected during the Follow-Up period of the Extension Phase.

Phase 2 – Expansion:

Subjects will be assigned by tumor type into 1 of 6 cohorts (minimum of 10 or 20 evaluable subjects per cohort) to receive the MTD, which was established as the RP2D in the Phase 1b portion of this study (lenvatinib 20 mg/day orally + pembrolizumab 200 mg Q3W, IV) to assess the safety and efficacy of the combination in the selected tumor-types. Each cohort will consist of subjects with one of the tumor types listed in the Phase 1b section above. Phase 2 is illustrated in Figure 2.

After the MTD is confirmed, and depending on the safety and efficacy observed, 6 cohorts will be enrolled (Figure 2). Each of these cohorts will only enroll subjects with one type of tumor (ie, NSCLC, predominantly clear cell RCC, EC, UC, melanoma (excluding uveal), HNSCC). RP2D combination doses will be administered. The intention is to enroll 20 subjects in each of the 6 cohorts. Data from the first 10 subjects in each cohort will be reviewed by the sponsor and investigators. At least 3 subjects must show response in order to determine continued enrollment up to 20 subjects.

The EC cohort may be further expanded to approximately 120 evaluable subjects. The decision to expand enrollment will be based on the results of 2 interim analyses that will take place when 21 and 60 subjects have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 21), if there are more than 3 responses, then approximately 40 additional subjects will be enrolled. At the second interim analysis (N = 60), if there are more than 12 responses, approximately 60 additional subjects will be enrolled. If there are 12 or fewer responses, the sponsor may decide whether to expand enrollment based on clinical outcome, eg, ORR and DOR.

The renal cell carcinoma cohort may be further expanded to approximately 145 total evaluable subjects to allow for approximately 100 evaluable subjects who have received 1 or 2 prior therapies that included an anti-PD-1/PD-L1 mAb. The decision to expand enrollment will be based on the results of 2 interim analyses. The first interim analysis will take place when 22 subjects (11 treatment naïve and 11 previously treated without an anti-PD-1/PD-L1 treatment) have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 22), if there are more than 5 responses, then approximately 45 additional subjects will be enrolled. It is anticipated that the additional 45 subjects will consist of approximately 12 treatment naïve subjects enrolled under Amendment 05 and approximately 33 previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies, and as of Amendment 07, the regimen with an anti-PD-1/PD-L1 mAb must be the most recent therapy. PD-1 treatment progression is defined by meeting all of the following criteria:

a) Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb.
b) Has demonstrated disease progression after PD-1/PD-L1 as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The initial evidence of PD is to

be confirmed by a second assessment no less than 4 weeks from the date of the first documented PD

c) Progressive disease has been documented within 12 weeks from last dose of anti-PD-1/PD-L1 mAb (refractory disease) or ≥12 weeks from last dose of anti-PD-1/PD-L1 mAb (late relapses)

The second interim analysis will include these 45 additional subjects and the 11 treatment naïve subjects included in the first interim analysis and will take place when these 56 subjects have sufficient follow-up to be evaluated for response. At the second interim analysis, whether the previously treated renal cell carcinoma subset will be further expanded will be decided based on clinical review of both efficacy and safety data.

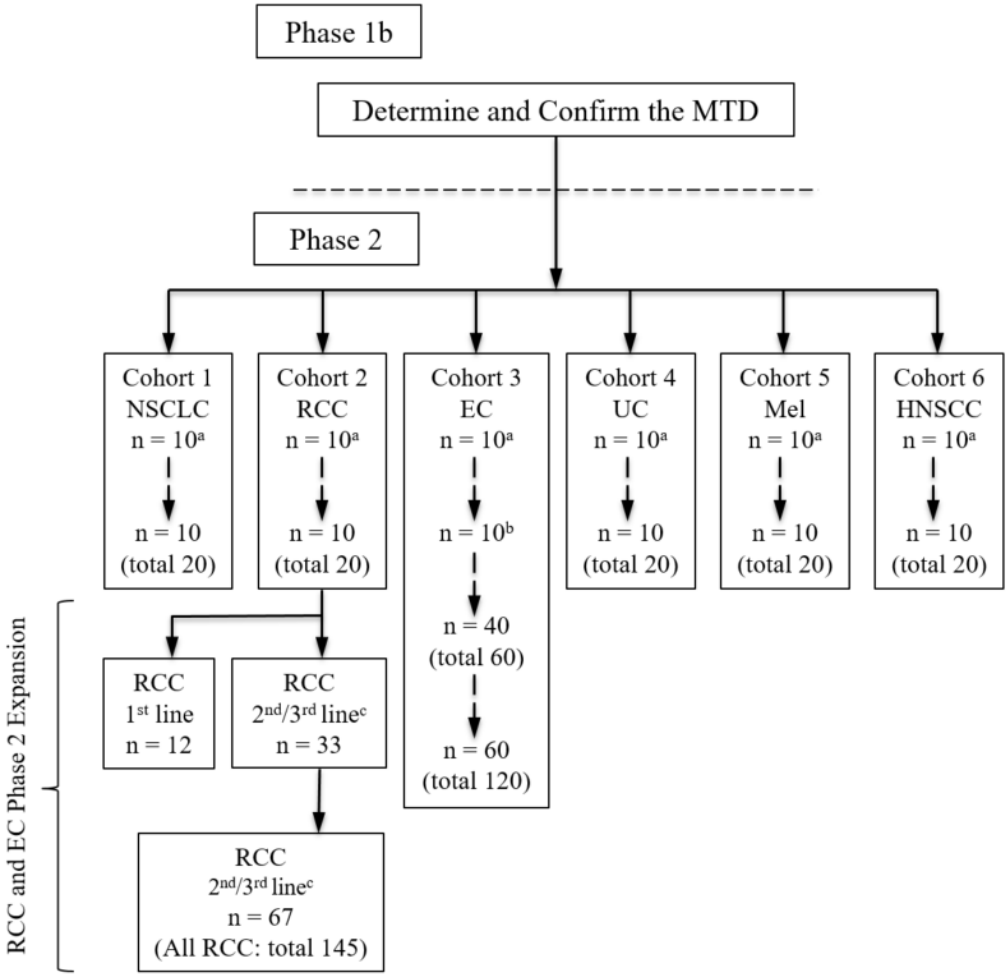


Figure 2 Phase 2 – Expansion In Selected Tumors

approx. = approximately EC = endometrial carcinoma; HNSCC = squamous cell carcinoma of head and neck; Mel = melanoma (excluding uveal); MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; ORR = objective response rate; RCC = renal cell carcinoma (predominantly clear cell), UC = urothelial carcinoma;

a: Based on the efficacy and safety results from the first 10 subjects in each cohort, an additional 10 subjects may be enrolled for a total of 20 subjects in each cohort.
b: The endometrial and renal cell carcinoma cohorts may be expanded to approximately 120 and 145 evaluable subjects, respectively.
c: This RCC subset includes previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti- programmed cell death protein 1 (PD)-1/ PD-1 ligand 1 (PD-L1) mAb.

Once they complete the Treatment Phase, each subject still receiving study treatment will transition into the Extension Phase. Tumor assessments will continue during the Treatment Period of the Extension Phase. As of Amendment 09, subjects in the treatment period of the extension phase who discontinue pembrolizumab for any reason and remain on lenvatinib study treatment will transition to lenvatinib commercial supply if local country regulations permit. As of Amendment 09, tumor assessments will continue during the Extension Phase as per the local standard of care but not less frequent than every 6 months. Tumor assessments will not be performed or collected during the Follow-Up period of the Extension Phase. Subjects who undergo the Off-Tx visit will undergo safety follow-up for AEs for 30 days from the last dose of study treatment. Serious adverse event (SAEs) will be collected for 90 days after the last dose or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. Transition to commercial lenvatinib will be considered new anticancer therapy. After the end of the safety follow-up period, no data will be collected subsequently. The data cutoff for each Phase 2 cohort will occur when the evaluable subjects in that cohort complete 8 cycles of treatment or discontinue early.

The study will be conducted in 3 phases: a Pretreatment Phase, a Treatment Phase, and an Extension Phase.

The definition of the end of the study for each cohort is the time of data cutoff for the final analysis or the time of last subject/last treatment, whichever occurs later.

9.1.1 Pretreatment Phase

The Prerandomization Phase will last for 28 days and will include a Screening Period and a Baseline Period.

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. 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. Tumor assessments performed up to 28 days prior to dosing are acceptable as screening tumor assessments if they are consistent with the requirements for this protocol.

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

9.1.1.2 Baseline Period

The purpose of the Baseline Period is to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Baseline assessments may be performed from Day -3 to Day -1 or on C (C) 1 D1 prior to dosing.

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

9.1.2 Treatment Phase

The Treatment Phase will begin with the administration of the first dose of study treatment to the first subject in Cycle 1 and continues in 21-day (3-week) cycles. The Phase 1b and Phase 2 Treatment Periods are described below:

9.1.2.1 Treatment Period

- **Phase 1b:** The Treatment Period for each subject ends after they complete Cycle 1 of treatment or they discontinue early. Those that discontinue study treatment in Cycle 1 transition to the Off Treatment (Off-Tx) Visit of the Follow-up Period of the Extension Phase. Those that complete Cycle 1 transition to the Treatment Period of the Extension Phase.

- **Phase 2:** The Treatment Period for each subject ends after they complete 8 cycles of treatment unless they discontinue early. Those that discontinue study treatment before completing 8 cycles transition to the Off-Tx Visit of the Follow-up Period of the Extension Phase. Those that complete 8 cycles transition to the Treatment Period of the Extension Phase.

9.1.3 Extension Phase

The Extension Phase consists of 2 periods, the Treatment Period and the Follow-up Period.

9.1.3.1 Treatment Period

Subjects still receiving study treatment at the end of the Treatment Phase will continue to receive the same study treatment in the Treatment Period of the Extension Phase. Those subjects that discontinue study treatment transition to the Off-Tx Visit of the Follow-up Period of the Extension Phase. Note that all AEs must be captured for 30 days after last dose of study medication.

9.1.3.2 Follow-Up Period

As of Amendment 9, the Follow-Up Period will consist of the Off-Tx Visit. No further visits will be conducted. The sponsor has decided to terminate survival follow-up for all subjects currently in survival follow-up.

Survival follow-up data will no longer be collected after the Off-Tx Visit and after 30 days from the last dose of study drugs.

The Follow-up Period consists of the Off-Tx Visit and the Follow-up Visits.

- The Off-Tx Visit will occur within 30 days after the last dose of study treatment. It applies to the Phase 1b subjects who discontinued study treatment early, before completing Cycle 1, and to the Phase 2 subjects who discontinued study treatment early, before completing 8 cycles. Following the completion of the Off-Tx Visit, subjects will transition to the Follow-up Period of the Extension Phase.

- In 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 survival, with tumor assessments performed as detailed in the Schedule of Procedures/Assessments, and subsequent anticancer treatments. Follow-up Visits continue as long as the study subject is alive unless the subject withdraws consent or until the sponsor terminates the study. The sponsor may decide to terminate survival follow-up anytime during the Extension Phase or when all subjects have discontinued study treatment.

9.2 Discussion of Study Design

The study design follows well-established designs for Phase 1b/2 oncology studies, including ongoing studies featuring co-administration of oncology drugs with different mechanisms of action and PD-1 inhibitors. The design allows for rapid identification of tumors types which will respond to the combination of a TKI with a PD-1 inhibitor. The tumor types to be studied in this study (NSCLC, renal cell carcinoma, EC, UC, HNSCC, or melanoma) have shown response to lenvatinib and/or a PD-1 inhibitor in other studies where the drug products were individually administered.

9.3 Selection of Study Population

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. The subjects from Phase 1b and Phase 2 will be enrolled at up to 25 sites from the US and the EU.

Phase 1b - Depending on the number of dose levels explored, Phase 1b will enroll between 10 and 30 evaluable subjects with selected solid tumors.

Phase 2 may enroll approximately 20 subjects in each cohort. The EC and the RCC cohorts may be further expanded to approximately 120 and 145 evaluable subjects, respectively.

9.3.1 Inclusion Criteria

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

1. Phase 1b: Histologically and/or cytologically confirmed metastatic selected solid tumor types that have progressed after treatment with approved therapies or for which there are no standard effective therapies available. If nivolumab or pembrolizumab is an approved therapy for the subject's tumor type, but the subject has not been treated with it, the Investigator may enroll the subject in this study.

   Phase 2: Histologically and/or cytologically confirmed metastatic selected solid tumor types with 0-2 prior lines of systemic therapy. If previously treated, subject has progressed after previous treatment.

   As of Amendment 03, for the NSCLC and melanoma cohorts, subjects must have progressed on or after prior treatment with one anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

   As of Amendment 05, for the RCC cohort, subjects are either treatment naïve or must have progressed on treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies.

   As of Amendment 06, for the RCC cohort, all subjects must have progressed on treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies, and as of Amendment 07, the regimen with an anti-PD-1/PD-L1 mAb must be the most recent therapy. PD-1 treatment progression is defined by meeting all of the following criteria:

   a. Has received at least 2 doses of an approved anti-PD-1/PD-L1 mAb
   b. Has demonstrated disease progression after PD-1/PD-L1 as defined by RECIST v1.1. The initial evidence of PD is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented PD
   c. Progressive disease has been documented within 12 weeks from last dose of anti-PD-1/PD-L1 mAb (refractory disease) or ≥12 weeks from last dose of anti-PD-1/PD-L1 mAb (late relapses)

   Selected tumor types of both phases: NSCLC, predominantly clear cell renal cell carcinoma, EC, UC, squamous cell carcinoma of the head and neck, or melanoma (excluding uveal melanoma).

2. Life expectancy of 12 weeks or more

3. Phase 2: Measurable disease meeting the following criteria:

   a. At least 1 lesion of ≥10 mm in the longest diameter (LDi) for a non-lymph node or ≥15 mm in the short-axis diameter for a lymph node that is serially measurable according to irRECIST using computerized tomography/magnetic resonance imaging (CT/MRI).

   b. Lesions that have had external beam radiotherapy or loco-regional therapies such as radiofrequency) ablation must show subsequent evidence of substantial size increase to be deemed a target lesion.

4. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1.

5. 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 prior to the C(C) 1 D1.

6. Adequate renal function defined as creatinine ≤1.5 × (upper limits of normal (ULN) or calculated creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula with creatinine levels >1.5 × ULN.

7. Adequate bone marrow function:

   - Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5 × 10^3/μL)
   - Platelets ≥ 100,000/mm^3 (≥100 × 10^9/L)
   - Hemoglobin ≥ 9.0 g/dL

8. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5.

9. Adequate liver function as evidenced by bilirubin ≤1.5 times the ULN and alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN). In case ALP is >3 × ULN (in the absence of liver metastases) or >5 × ULN (in the presence of liver metastases) AND the subject also is known to have bone metastases, the liver specific ALP isoenzyme must be separated from the total and used to assess the liver function instead of the total ALP.

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

11. Subjects with known brain metastases will be eligible if they have completed the primary brain therapy (such as whole brain radiotherapy, stereotactic radiosurgery or complete surgical resection) and if they have remained clinically stable, asymptomatic and off of steroids for at least 28 days before starting study treatment.

12. All females must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin [β-hCG]) at the Screening Visit and the Baseline Visit. A pregnancy test needs to be performed within 72 hours of the first dose of study drug. Females of childbearing potential* must 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

- 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.

13. Male subjects who are partners of women of childbearing potential must use a condom + spermicide and their female partners if of childbearing potential must use a highly effective method of contraception (see methods described in Inclusion Criterion #12) beginning at least 1 menstrual cycle prior to starting study drug(s), throughout the entire study period, and for 120 days after the last dose of study drug, unless the male subjects are totally sexually abstinent or have undergone a successful vasectomy with confirmed azoospermia or unless the female partners have been sterilized surgically or are otherwise proven sterile.

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

15. Archival tumor tissue or a newly obtained biopsy must be available prior to the first dose of study drug for biomarker analysis. In the case archival tissue cannot be provided, patients with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the sponsor.
    Note: In case of submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut. See Section 9.5.1.4.2 in the protocol for an explanation.

9.3.2 Exclusion Criteria

1. Prior anticancer treatment within 28 days (or 5 times the half-life, whichever is shorter) or any investigational agent within 30 days prior to the first dose of study drugs. All acute toxicities related to prior treatments must be resolved to Grade ≤1.

2. Subjects must have recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.

3. Subjects having >1+ proteinuria on urinalysis will undergo 24-hour urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24-hour will be ineligible.

4. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib

5. New York Heart Association (NYHA) congestive heart failure of grade II or above, unstable angina, myocardial infarction within the past 6 months, or serious cardiac arrhythmia associated with significant cardiovascular impairment within the past 6 months

6. Prolongation of QTc interval to >480 msec

7. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug

8. Active infection (any infection requiring systemic treatment)

9. Subject is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C

10. Serious nonhealing wound, ulcer, or bone fracture

11. Known intolerance to either of the study drugs (or any of the excipients)

12. History of organ allograft (subject has had an allogenic tissue/solid organ transplant)

13. Biologic response modifiers (eg, granulocyte colony-stimulating factor within 4 weeks before study entry. Chronic erythropoietin therapy is permitted provided that no dose adjustments were made within 2 months before first dose of study treatment.

14. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical study

15. Females who are pregnant or breastfeeding

16. Excluding the primary tumor leading to enrollment in this study, any other active malignancy (except for definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the bladder or cervix) within the past 24 months

17. Prior treatment with lenvatinib (no exceptions) or any PD-1, anti-PD-L1, or anti-PD-L2 agent, except:

- the melanoma and NSCLC cohorts, where prior treatment with one anti-PD-1, anti-PD-L1, or anti-PD-L2 agent is allowed.
- the previously treated renal cell carcinoma subjects (as of Amendment 05) where prior treatment with one regimen containing an anti-PD-1/PD-L1 mAb is required.

18. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids (up to 7.5mg/d of prednisone or equivalent) may be approved after consultation with the sponsor.

19. No active autoimmune disease 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.

20. Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis

21. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

9.3.3 Removal of Subjects From Therapy or Assessment

As of Amendment 09, the Follow-Up Period will consist of the Off-Tx Visit. No further visits will be conducted. The sponsor has decided to terminate survival follow-up for all subjects currently in survival follow-up.

Survival follow-up data will no longer be collected after the Off-Tx Visit and after 30 days from the last dose of study drugs.

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-tx 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-tx 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 Discontinuation From Treatment CRF page will be completed indicating the primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from treatment. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing CRF page.

During the Follow-Up Period, subjects who have discontinued study treatment without progression should have disease assessments until disease progression is documented or another anticancer therapy is initiated.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis. As of Amendment 09, survival follow-up data will no longer be collected.

9.4 Treatments

9.4.1 Treatments Administered

9.4.1.1 Lenvatinib

Lenvatinib will be administered with water orally once a day (with or without food) in 21-day cycles at approximately the same time each day. Treatment cycles will be counted continuously regardless of dose interruptions. On (D1) of each cycle, it will be administered approximately 1 hour after completion of pembrolizumab administration.

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

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib-related toxicity will be in accordance with the guidelines provided in Table 2. Once the dose has been reduced, it may not be increased at a later date.

For management of hypertension and proteinuria, refer to main protocol text for instructions before consulting the table below, as appropriate. (See Table 3 for dose reductions. Any dose reduction below 4 mg/day must be discussed with the sponsor. Once the dose has been reduced, it cannot be increased at a later date.) Dose reductions of lenvatinib in Phase 2 occur in succession starting at the RP2D dose identified in Phase 1b.

Table 2 Dose Modifications for Lenvatinib Treatment-Related Toxicity

Lenvatinib Treatment-Related Toxicity[a,b]	During Therapy	Adjusted Dose[f]
Grade 1, Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d] and Grade 3[g]		
First occurrence	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib by one dose level[b]
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib by one more dose level
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib by one more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib by one more dose level

Grade 4[e,g]: Discontinue lenvatinib

a. An interruption of lenvatinib treatment for more than 21 days (due to lenvatinib treatment-related toxicities) will require a discussion with the sponsor before treatment can be resumed.
b. Excluding alopecia. Initiate optimal medical management for nausea, vomiting, hypothyroidism, hypertension and/or diarrhea prior to any lenvatinib interruption or dose reduction. For treatment-related hypertension, refer to Management of Hypertension (Section 9.4.1.1.2) for dose modification guidelines.
c. Applicable only to Grade 2 toxicities judged by subject and/or physician to be intolerable.
d. Obese subjects with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1 weight loss). These subjects will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal body mass index (BMI) (if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
f. Refer to Table 3 for adjusted dose.
g. For asymptomatic Grade ≥3 elevations of amylase and lipase, the sponsor's medical monitor should be consulted to obtain permission to continue treatment.

General guidelines for holding periods of lenvatinib due to procedures:

For minor procedures, lenvatinib should be stopped 2 days before the procedure and restarted 2 days after, once there is evidence of adequate healing and no risk of bleeding. Needle biopsies (fine needle aspirations and core needle aspiration) are usually considered minor procedures.

For major procedures, lenvatinib should be stopped at least 1 week (5 half-lives) before the procedure and then restarted once there is clear wound healing and no risk of bleeding, but at least 2 weeks after the procedure. It is up to the investigator to determine if it is a major or minor procedure. Usually a major procedure implies general anesthesia.

Table 3 Dose Reduction Recommendations for Lenvatinib Treatment-Related Toxicity

Initial Lenvatinib Dose (mg, QD)	Adjusted Dose To Be Administered (mg, QD)			
	Reduction 1	Reduction 2	Reduction 3	Reduction 4
24	20	14	10	8[a]
20	14	10	8	4[a]
14	10	8	4[a]	

QD = once a day
a. Consult sponsor for further dose reduction recommendations.

9.4.1.1.2 MANAGEMENT OF HYPERTENSION

Hypertension is a recognized side effect of treatment with drugs inhibiting vascular endothelial growth factor (VEGF) signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib 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 C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments a minimum of 1 hour apart. One BP assessment is defined as the mean value of 3 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 a minimum of 1 hour apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists. For subjects with hypertension and proteinuria, appropriate therapy, eg, angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist, is preferred (Kilfoy, et al., 2009).

Lenvatinib should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the subject has been on the same hypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

During the Treatment Period, both in the Treatment Phase and in the Extension Phase, 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 clinical indicated until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 3 consecutive months. 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 3 consecutive months.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on repeat measurements after 1 hour:

1. Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving antihypertensive medication
2. For those subjects already on antihypertensive medication, 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 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted. It should be restarted at one lower dose level as specified in Table 3 only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours

- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at an additional dose reduction as specified in Table 3 only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at a third dose reduction as specified in Table 3 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.

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

- Institute appropriate medical management
- Discontinue study drug

9.4.1.1.3 MANAGEMENT OF PROTEINURIA

Regular assessment of proteinuria should be conducted as detailed in the Schedule of Procedures/Assessments (Table 8). Guidelines for assessment and management of proteinuria:

1. Grading will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to instructions contained in Table 2,"Dose Modifications for Lenvatinib Treatment-Related Toxicity,"
2. A 24-hour urine collection (within 72 hours) to verify the grade of proteinuria for protein quantitation is required in the following situations:
   - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug
   - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
   - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is 2+, 3+, or 4+
3. Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months.

Grading of proteinuria should be performed according to CTCAE v4.03 (Appendix 3) but will be based on the 24-hour urine collection for total protein result, if a 24-hour urine was performed at that time point.

For subjects with lenvatinib-related toxicity, the dose reduction and/or interruption instructions provided in Table 2 of the study protocol should be followed.

9.4.1.1.4 MANAGEMENT OF HEPATOTOXICITY

Regular monitoring of liver function tests (eg, 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 occur indicating a decrease in liver function by 1 grade or more from baseline, the instructions contained in Table 2 of the protocol should be followed, "Study Treatment Dose Reduction and Interruption Instructions". Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

9.4.1.1.5 MANAGEMENT OF THROMBOEMBOLIC EVENTS

Subjects should be advised to pay attention to the symptoms suggestive of venous thromboembolic events, which include acute onset of dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, redness and warmth to touch or tenderness. In case any of these signs or symptoms appear, subjects should be instructed to report such signs and symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 2 of the protocol should be followed, "Study Treatment Dose Reduction and Interruption Instructions." 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.

9.4.1.1.6 MANAGEMENT OF POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of lenvatinib-treated subjects. Posterior reversible encephalopathy syndrome 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. An MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure. In subjects with signs or symptoms of PRES, dose interruptions, reductions, or discontinuation may be required per instructions included in Table 2. Please refer to Section 7 of the Investigator's Brochure for further information on lenvatinib, including the full set of special warnings and precautions for use (Section 7.4.4).

9.4.1.1.7 MANAGEMENT OF HYPOCALCEMIA

Serum calcium should be monitored every 3 weeks per the Schedule of Procedures/Assessments. Hypocalcemia should be treated per institutional guidelines (eg, using, as appropriate, calcium, magnesium, and Vitamin D supplementation) until resolution.

9.4.1.1.8 MANAGEMENT OF QT PROLONGATION

Lenvatinib should be withheld in the event of development of QT interval prolongation ≥ 500 msec. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium, and replenish as appropriate.

9.4.1.1.9 MANAGEMENT OF OSTEONECROSIS OF THE JAW

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of osteonecrosis of the jaw (ONJ). Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution.

9.4.1.2 Pembrolizumab

Pembrolizumab (200 mg) will be administered as a 30-minute IV infusion, Q3W (infusions lasting between 25 minutes to 40 minutes are acceptable). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

Study treatment with pembrolizumab may be administered up to 3 days before or after the scheduled D1 of each cycle due to administrative reasons.

Adverse events (both nonserious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4 below. See Section 9.4.1.2.1 for supportive care guidelines, including use of corticosteroids.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Event	Toxicity Grade (CTCAE v4.0)	Action with Pembrolizumab	Corticosteroids and/or Other Therapies	Monitoring and Follow-up
General instructions: 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. **If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.**				
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Recurrent Grade 2, 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	Monitor participants 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). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants 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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Event	Toxicity Grade (CTCAE v4.0)	Action with Pembrolizumab	Corticosteroids and/or Other Therapies	Monitoring and Follow-up
AST or ALT elevation or Increased Bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper. Administer corticosteroids (initial dose of 1 to 2 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[a]	Initiate insulin replacement therapy for participants with T1DM. Administer anti-hyperglycemic in participants with hyperglycemia.	Monitor participants 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, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue		

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Event	Toxicity Grade (CTCAE v4.0)	Action with Pembrolizumab	Corticosteroids and/or Other Therapies	Monitoring and Follow-up
or acute kidney injury.				
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 2, 3 or 4	Permanently discontinue		
All other immune-related AEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes.
	Grade 3	Withhold or discontinue based on event[b].		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s) = adverse event(s), ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, DRESS = Drug Rash with Eosinophilia and Systemic Symptom; GI = gastrointestinal, IO=immuno-oncology; irAE = immune-related adverse event, IV = intravenous, SJS = Stevens-Johnson Syndrome; T1DM = Type 1 diabetes mellitus; TEN = Toxic Epidermal Necrolysis; ULN = upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the subject's study record.

9.4.1.2.1 SUPPORTIVE CARE GUIDELINES FOR PEMBROLIZUMAB

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 9.4.1.2. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional antiinflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Section 9.4.1.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform additional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 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	Subject may be premedicated 1.5h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine).

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	deemed medically stable in the opinion of the investigator. If symptoms resolve within one 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.**	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) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids 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. ****In cases of anaphylaxis, epinephrine should be used immediately.** **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Table 5 Infusion Reaction Treatment Guidelines		
NCI CTCAE Grade	**Treatment**	**Premedication at subsequent dosing**

ANC = absolute neutrophil count, CTCAE = Common Terminology Criteria for Adverse Events v4.03, h = hour, IV = intravenous, NCI = National Cancer Institute, NSAID = nonsteroidal antiinflammatory drug.

9.4.2 Identity of Investigational Products

Lenvatinib and pembrolizumab will be supplied by the sponsor in appropriately labeled containers.

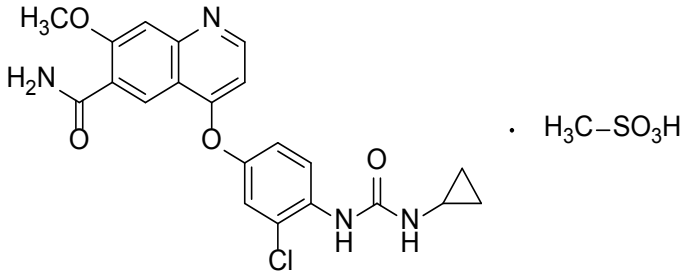
Lenvatinib will be provided as 4-mg and 10-mg capsules. Lenvatinib is formulated with calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, and talc.

Pembrolizumab may be provided as a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial will be reconstituted and diluted for IV infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate-80 (0.4 mg), sucrose (140 mg). The solution may contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Alternatively, pembrolizumab may be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV 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.

9.4.2.1 Chemical Name, Structural Formula of Lenvatinib

LENVIMA is the mesylate salt of lenvatinib. Its chemical name is 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6 carboxamide methanesulfonate. The molecular formula is C21H19ClN4O4 • CH4O3S, and the molecular weight of the mesylate salt is 522.96. The chemical structure of lenvatinib mesylate is:



9.4.2.2 Information of Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) mAb with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with

programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

9.4.2.3 Labeling for Study Drug

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

9.4.2.4 Storage Conditions

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

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will receive lenvatinib in combination with pembrolizumab. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

For the assessment of MTD, the lenvatinib doses selected are 24 mg, 20 mg, and 14 mg QD all in combination with 200 mg pembrolizumab Q3W given IV. While 24 mg is the recommend dose for locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (LENVIMA Package Insert/SmPC), 20 mg and 14 mg are the first and second doses in lenvatinib's dose reduction scheme for all tumors (except hepatocellular carcinoma) for which data are available. While 2 mg/kg is the recommended dose for pembrolizumab for melanoma (KEYTRUDA Package Insert/SmPC), a 200 mg Q3W fixed dose regimen is planned to be used in this study (see Section 7.2).

9.4.5 Selection and Timing of Dose for Each Subject

Lenvatinib will be administered with water orally once a day (with or without food) in 21-day cycles at approximately the same time each day. Treatment cycles will be counted continuously regardless of dose interruptions. On D1 of each cycle, it will be administered approximately within 1 hour after completion of pembrolizumab administration.

Pembrolizumab will be administered as a dose of 200 mg as a 30-minute IV infusion, Q3W (infusion durations of 25 minutes to 40 minutes are acceptable). 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 D1 of each cycle due to administrative reasons.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

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

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

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 lenvatinib or pembrolizumab may be continued during the study.

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

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

The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered.

9.4.7.1 Drug–Drug Interactions

Lenvatinib's weak in vitro inhibitory and induction potential on cytochrome P450 (CYP) 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 an important enzyme responsible for human hepatic metabolism of lenvatinib. However, clinical studies conducted to test these findings showed that co-administration of lenvatinib with CYP3A4/P-glycoprotein (P-gp) inhibitors or inducers is not of clinical concern (see Appendix 5 for a summary of clinical findings).

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

9.4.7.2 Prohibited Concomitant Medications/Vaccinations

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on study therapy or vaccination schedule requires the mutual agreement of the investigator, the sponsor, and the subject.

9.4.7.2.1 PROHIBITED CONCOMITANT MEDICATIONS

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies, such as chemotherapy, hormone therapy, palliative radiotherapy, or immunotherapy, this will be judged to represent evidence of disease progression, and continuation of the study medication and further participation in the study must be discussed and agreed upon with the sponsor.

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

- Anticancer therapies such as chemotherapy, TKIs, antitumor interventions (surgical resection, thoracocentesis, etc.), or immunotherapy
- Investigational agents other than lenvatinib and pembrolizumab
- Radiation therapy

Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered as an exception on a case by case basis after consultation with the Sponsor. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacille Calmette-Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the sponsor.

Note: 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. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this clinical study.

For clarification, the following concomitant medications are also **allowed**:

- Thyroid hormone suppressive therapy (including therapy to treat hypothyroidism and hyperthyroidism)
- Adjuvant hormonal therapy for history of definitively treated breast or prostate cancer
- Anticoagulants including LMWH, warfarin, anti-Xa agents
- Antiinflammatory agents (n.b., use of steroids is not permitted except as outlined in Sections 9.4.1.2.1 to manage immune-related AEs)
- Bisphosphonates or denosumab
- Supportive care guideline for pembrolizumab (see Section 9.4.1.2.1)
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the patient has been enrolled)

9.4.8 Treatment Compliance

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

9.4.9 Drug Supplies and Accountability

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

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated 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 or medical registration number on the CV
- A signed and dated clinical studies agreement

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

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

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). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator 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

All study-related medical or dental decisions must be made by an investigator who is a qualified physician.

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 and ethnicity. Baseline characteristics will include ECOG-PS, NYHA cardiac disease classification, and pathological tumor-node-metastasis (pTNM) staging at initial diagnosis (Appendix 2 and Appendix 4). FIGO grade (Creasman, 2009) will be collected from all EC subjects if available. The Karnofsky performance status (KPS) (Appendix 8) will also be collected from all RCC subjects only to permit the calculation of the International Metastatic Renal Cell Carcinoma Database Consortium prognostic risk group (Favorable, Intermediate, or Poor) (Ko, et al., 2015; Heng, et al., 2013; Heng, et al., 2009).

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All clinically significant medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations will be performed as designated in the Schedule of Procedures/ Assessments (Table 8 and Table 9). A comprehensive physical examination including oral examination will include evaluations of the head, eyes, ears, nose, throat, jaws, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.3 Efficacy Assessments

All efficacy endpoints, other than OS, will be based on the tumor assessments performed by the investigators using both irRECIST and modified RECIST 1.1. **Treatment decisions by the Investigator will be based on irRECIST.** All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans from Phase 1b must be accessible in the event of a sponsor request to submit them for central review. For Phase 2, images acquired for tumor assessments will be sent to an imaging core laboratory (ICL)for archiving and potential independent analysis. As of Amendment 3, tumor assessment scans for the EC subjects will be assessed by IIR. As of Amendment 5, tumor assessment scans for the renal cell carcinoma subjects will also be assessed by IIR. As of Amendment 08, scans acquired after data cutoff for final efficacy analysis, in any cohort, will no longer be sent to the ICL.

Renal Cell Carcinoma PD-1 pre-treated cohort

As of Amendment 08, for subjects enrolled in the RCC cohort who were previously treated with anti-PD-1/PD-L1 mAb, available pre-Baseline scans will be collected by sites and sent to an ICL designated by the sponsor for quality assessment and archival, and potential future independent review.

Pre-Baseline scans in this context are as follows:

- nadir scan on prior anti-PD-1/PD-L1 mAb therapy (additional scans on prior anti-PD-1/PD-L1 mAb therapy may be submitted if the nadir scan is unavailable);
- initial progression on prior approved anti-PD-1/PD-L1 mAb therapy;
- confirmed progression on prior anti-PD-1/PD-L1 mAb therapy (preferably no less than 4 weeks from the date of the first documented PD, as of Amendment 7).

As of Amendment 09, pre-baseline scans for RCC subjects are not required.

Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks (during the 6th week; counting from C1D1) until Week 24, then every 9 weeks during treatment cycles in both the Treatment Phase and the Extension Phase. As of Amendment 09, tumor assessments will continue during the Extension Phase as per local standard of care but not less frequent than every 6 months. Tumor assessments will not be collected during the Follow-Up period of the Extension Phase. CT/MRI scans of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to C1 D1), at all tumor assessment time points, and as indicated clinicallyand as per local standard

of care. Color photographs containing a millimeter scale must be taken of all skin lesions being used as target lesions. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable. Subjects with HNSCC must also have head and neck scans performed.

The computed tomography (CT) scan should be a diagnostic quality spiral or multidetector CT with oral and iodinated IV contrast, and the MRI scan should be performed with IV gadolinium chelate. Scans of the neck, abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest must be done with CT. If iodinated IV contrast is contraindicated, the chest evaluation should be done with non-contrast CT, and the abdomen and pelvis evaluation should be performed using either CT with oral contrast (without IV contrast) or MRI with gadolinium chelate IV contrast (the latter is preferred). Spiral/multidetector CT should be performed with a 5-mm contiguous slice reconstruction algorithm. If body MRI scans are performed, contiguous slices of 5 mm are also recommended.

Low-dose non-contrast CT transmission scans from a positron emission tomography-CT (Positron emission tomography [PET]-CT) combination scanner are not acceptable. Ultrasound should not be used for radiographic tumor assessment. Chest disease may not be followed using chest x-ray.

A brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at screening to assess potential CNS disease and/or metastases. For subjects with previously treated eligible brain metastases, a brain scan must be performed at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm immune-related complete response (irCR) within 1 week of response confirmation, or if clinically indicated.

The tumor assessment schedule should not be affected by interruptions in study treatment.

Subjects going Off-Tx without disease progression will also undergo tumor assessments per the Schedule of Procedures/Assessments until disease progression is documented or another anticancer therapy is initiated.

The same method of assessment used at screening must be used at all time points. Throughout the study it is critical that the same imaging methodology be applied and contrast be consistently provided unless IV contrast becomes medically contraindicated during the course of treatment or the dose of contrast needs to be adjusted based on the subject's health status.

Bone scans will be performed for all subjects (except for subjects with HNSCC) at screening, every 24 weeks, or sooner if clinically indicated, and at confirmation of irCR. A bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases will be performed within 6 weeks prior to C1D1 (historical scans are acceptable) and then every 24 weeks (within that 24th week) from C1D1 for all tumor types except for HNSCC, or sooner if clinically indicated. For those visits where the bone scan

does not coincide with the schedule for the acquisition of the CT/MRI scans (ie, Weeks 48 and 72), the bone scan should be added to the closest CT/MRI time point (eg, Weeks 51 and 69). In subjects whose body CT/MRI scans indicate that irCR has been achieved, except for subjects with HNSCC, a bone scan will be required at confirmation of irCR to exclude new bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging.

In order for immune-related stable disease (irSD) to be considered the best overall response, it must occur ≥5 weeks following the first dose of study drug.

The first radiological assessment of tumor response status will be performed at Week 6 (±1 week), unless there is clinical indication warranting earlier radiologic imaging. If imaging at Week 6 shows irSD, treatment will be continued and tumor assessments will be conducted at the next regularly scheduled imaging time point, ie, at Week 12 (±1 week). Responses (immune-related partial response [irPR] or irCR [complete response]) should be confirmed no less than 4 weeks after the initial response, but generally at the next scheduled tumor assessment time point.

If the time point tumor assessment is PD, treatment should continue and tumor assessments repeated at least 4 weeks later, but generally at the next scheduled tumor assessment time point in order to confirm immune-related progression disease (irPD). If repeat imaging shows a reduction in the tumor burden compared to the initial tumor assessment demonstrating PD, treatment may be continued as per treatment schedule. If repeat imaging confirms irPD, subjects will be discontinued from study treatment. In determining the tumor time point response, investigators should consider all target lesions as well as nontarget lesions and new lesions.

The decision to continue study treatment after the first evidence of PD is at the Investigator's discretion based on the clinical status of the subject as described in Table 6 below.

Subjects may continue receiving study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG PS
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

If irPD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact Sponsor to discuss continuing treatment.

Tumor assessments per modified RECIST 1.1 will follow Eisenhauer, et al. (2009), however, up to 10 target lesions, up to 5 per organ, may be selected (as opposed to the maximum of 5 target lesions, up to 2 per organ, mentioned in Eisenhauer, et al., 2009).

Table 6 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥4 weeks (next TA time point) to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scans	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Subsequent scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Subsequent scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

CR = complete response, PR = partial response, SD = stable disease, PD = progression disease, N/A = not applicable.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

A schedule of lenvatinib PK, pharmacodynamic, and pharmacogenomic sampling is shown in the Schedule of Procedures/Assessments (Table 8 and Table 9).

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Plasma concentrations of lenvatinib will be measured.

Blood samples will be collected as specified in Table 8 and Table 9. See the Laboratory Manual for a description of collection, handling, and shipping procedures for PK samples.

Samples from all subjects will be analyzed. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry (LCMS/MS) methodology using a previously validated assay.

Blood will also be drawn where possible at the first report of a serious adverse event (SAE) or severe unexpected AE and at its resolution.

A population PK model for lenvatinib will be developed using the program NONMEM. The model will be parameterized in terms of clearance and volume of distribution

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

A schedule of biomarker sampling is shown in the Schedule of Procedures/Assessments (Table 8 and Table 9).

Blood samples for the development of exploratory predictive biomarkers will be collected prior to the first dose of study drug, on C1D15, and on D1 of all subsequent cycles during Treatment Phase, and at the Off-Tx assessment. Subjects will be required to provide an archival tumor tissue sample and/or a fresh biopsy of tumor before treatment for biomarker analyses (patients with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the sponsor). For subjects in the NSCLC cohort every effort is to be made to obtain a fresh biopsy of tumor at the beginning of C2 (optional for other cohorts on study) if they have recovered adequately from the biopsy taken prior to starting therapy and to provide the acquired tissue for these biomarker analyses. Biomarker discovery and/or validation will be performed to identify blood or tumor biomarkers which may be useful to predict subject response to lenvatinib and/or pembrolizumab, as determined by evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Blood samples from subjects receiving lenvatinib and pembrolizumab may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods or new technology. In addition, biomarkers identified in other lenvatinib clinical studies may also be assessed in the biomarker 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.

Archived, formalin-fixed paraffin-embedded (FFPE) tissue or a newly obtained biopsy will be collected from all subjects for potential assessment of mutations and other genetic alterations and/or proteins including PD-1/PD-L1 status and other relevant biomarkers (eg, tumor infiltrating lymphocytes, T-cell repertoire, ribonucleic acid [RNA] signature profiles), which may be important in the development and progression of cancer as well as for potential use in diagnostic development. Appropriate technology/methodologies will be used based on the amount of tumor tissue available.

Note: For PD-1/PD-L1 status, submission of FFPEtumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from the site slide sectioning date; otherwise, a new specimen will be requested.

As of Amendment 06, available known mutation status, including mismatch repair (MMR) or microsatellite instability (MSI) status, will be collected on the electronic case report form (eCRF).

For all tumor types except NSCLC, optional fresh paired tumor biopsies will be collected from consented subjects to examine markers including markers of target engagement, relevant pharmacodynamic biomarkers, and potential markers of response. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; liver metastases which can be readily accessed using CT guidance). Subjects should have the biopsy before administration of the first dose of study drug and at a time point 3-6 weeks after the first dose (if they have recovered adequately from the biopsy taken prior to starting therapy). For NSCLC every effort is to be made to obtain a fresh tumor biopsy; subjects will have fresh tumor biopsies collected from consented subjects before administration of the first dose of study drug and at a time point 3-6 weeks after the first dose (if they have recovered adequately from the biopsy taken prior to starting therapy).

As of Amendment 01, a blood sample for peripheral blood mononuclear cells (PBMCs) and plasma isolation will be collected from enrolled subjects. Cell free nucleic acid isolated from plasma samples may be used to obtain circulating tumor DNA (ctDNA) and explore tumor genetic alterations such as mutations observed in archival tumor samples as well as those which develop during drug treatment.

In Phase 2, as of Amendment 4, a blood sample for nucleic acid analysis will be collected for potential assessment of gene expression profiling. In Phase 2, as of Amendment 3, a blood sample will be collected for potential pharmacodynamics and pharmcogenomic analysis. Variation in lenvatinib exposure or the occurrence of AEs observed in the study population may be evaluated by correlating single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor, for potential microsatellite instability analysis, and for potential immune response monitoring. Data obtained will be used for research to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib/pembrolizumab, cancer and/or for potential diagnostic development.

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

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades (for both increasing and decreasing severity), and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; echocardiograms or multigated acquisition (MUGA) scans including left ventricular ejection fraction (LVEF); and performance of physical examinations including oral examinations as detailed in Section 9.5.1.2.1.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

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

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 and for 30 days after the last dose of study treatment. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported. SAEs will be collected for 90 days after the last dose or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. An AE will not be reported on the Adverse Event CRF if other anticancer treatment is started. All SAEs will be reported on the Adverse Event CRF. All deaths will be collected for 30 days following the last dose of study treatment and reported on the Survival CRF.

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.

Progression of malignant disease (PD) should not be recorded as an AE in studies where it is included as an endpoint for underlying disease. If the progression leads to an untoward medical occurrence (increased pain, pleural effusion, etc), then this medical occurrence should be the AE.

All AEs must be followed for 30 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

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

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to Common Terminology Criteria for Adverse Event (CTCAE v4.03) (Appendix 3). 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.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

A 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 AE 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.

Events of clinical interest for this study include:

1. an elevated AST or ALT laboratory value that is greater than or equal to 3 × ULN and an elevated total bilirubin lab value that is greater than or equal to 2 × ULN and, at the same time, an ALP laboratory value that is less than 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent). It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and ALP that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not events of clinical interest for this trial.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; and 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 AE (ie, there is no untoward medical occurrence) associated with the hospitalization:

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

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 7. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 8 and Table 9) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 7 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential INR[b]
Clinical Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, magnesium, phosphorus, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function tests	Blood urea nitrogen, creatinine
Thyroid function tests[a]	TSH and free T4 levels
Other	Albumin, cholesterol, glucose, lactate dehydrogenase, total protein, triglycerides, amylase, lipase
Urinalysis	Glucose, ketones, pH, protein, RBCs, specific gravity

RBC = red blood cell, T4 = thyroxine, WBC = white blood cell, INR, International Normalized Ratio.

a. Thyroid function will be assessed every 2 cycles.
b. Only at screening/baseline and when clinically indicated.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines (CCG). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 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 8 and Table 9) by a validated method. Blood pressure and heart rate will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart.

For subjects with an elevated BP (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), confirmation should be obtained by performing two assessments a minimum of 1-hour apart.

Subjects with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored every 2 weeks (on D1 and Day 15 or more frequently, as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months. See subsection for management of hypertensive subjects (Section 9.4.1.1.2).

Height will be measured at the Screening Visit only.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Physical examinations including oral examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 8 and Table 9). Documentation of the physical and oral examination will be included in the source documentation at the site. Only changes from screening physical or oral examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 8 and Table 9). 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 or sitting for a period of 5 minutes prior to the ECG. The Fridericia correction method for calculating QTc will be used.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CCGs. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

QT prolongation has been seen in some lenvatinib studies. Monitor electrocardiograms every cycle (as specified in the Schedule of Assessments) in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Refer to the Lenvatinib package insert.

9.5.1.5.7 Echocardiogram or Multiple Gated Acquisition Scan

A MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess LVEF as designated in the Schedule of Procedures/Assessments (Table 8 and Table 9). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

All scans performed during the study should be archived in accordance with the standard local practice. They must be accessible in the event of a sponsor request to submit them for central review.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 8 (Phase 1b) and Table 9 (Phase 2) present the schedule of procedures and assessments for the study.

Table 8 Phase 1b: Determination of the Maximum Tolerated Dose: Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

CRF	Phase	Pretreatment		Treatment			Extension			
	Period	Screening[a,b]	Baseline[a,b]	Treatment (Cycle 1[b])			Treatment (Cycle 2[b] & Beyond)		Follow-Up Period[bb]	
	Visit	1	2	3	4	5	6, 8, 10, 12, etc.	7, 9, 11, 13, etc.	Off-Treatment Visit[u]	Follow-up Visits (Off-Tx Visit + 1 day & Beyond)
	Day	-28 to -3	-3 to -1	1	8	15	1	15	+30 days after last dose	Every 12 weeks[y]
	Assessments									
S	Informed consent	X								
S	Inclusion/exclusion	X	X							
S	Demographic data	X								
S	ECOG PS/NYHA[c]	X	X				X		X	
	KPS[c]	X								
S	pTNM staging at diagnosis	X								
NS	Medical/surgical history	X	X							
S	Prior medications	X								
S	Vital signs[d]	X	X	X		X	X[d]	X[d,w]	X	
NS	Physical examination[e]	X	X[f]			X	X		X	
NS	12-lead ECG[g]	X		X			X		X	
S	MUGA scan or echocardiogram[z]	X		X[z]						
S	Clinical chemistry & hematology[i]	X	X			X	X		X	

Table 8 Phase 1b: Determination of the Maximum Tolerated Dose: Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

CRF	Phase	Pretreatment		Treatment			Extension			
	Period	**Screening[a,b]**	**Baseline[a,b]**	**Treatment (Cycle 1[b])**			**Treatment (Cycle 2[b] & Beyond)**		**Follow-Up Period[bb]**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**Off-Treatment Visit[u]**	**Follow-up Visits (Off-Tx Visit + 1 day & Beyond)**
	Day	-28 to -3	-3 to -1	1	8	15	1	15	+30 days after last dose	Every 12 weeks[y]
	Assessments									
S	Thyroid function tests[i]	X	X				X		X	
S	Urinalysis (Dipstick)[j]	X	X			X	X	X[x]	X	
S	Pregnancy test[k]	X	X							
S	Lenvatinib treatment			Throughout						
NS	Pembrolizumab treatment[aa]			X			X			
NS	Lenvatinib PK blood samples[l]			X		X	X			
S	Tumor assessments: CT (MRI)[m]	X		Counting from C1D1, for the first 24 weeks, during Week 6, 12, 18, and 24 (±1 week), or sooner, if clinically indicated, until documentation of confirmed PD. After 24 weeks, tumor assessments must be performed every 9 weeks counting from C1D1 (during Week 33, 42, 51, 60, etc.) (±1 week), or sooner if clinically indicated, until documentation of confirmed PD. Responses and PD must be confirmed at least 4 weeks later					X (unless done within previous 4 weeks) or subject discontinued for PD	X[m]

Table 8 Phase 1b: Determination of the Maximum Tolerated Dose: Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

CRF	Phase	Pretreatment		Treatment			Extension			
	Period	Screening[a,b]	Baseline[a,b]	Treatment (Cycle 1[b])			Treatment (Cycle 2[b] & Beyond)		Follow-Up Period[bb]	
	Visit	1	2	3	4	5	6, 8, 10, 12, etc.	7, 9, 11, 13, etc.	Off-Treatment Visit[u]	Follow-up Visits (Off-Tx Visit + 1 day & Beyond)
	Day	-28 to -3	-3 to -1	1	8	15	1	15	+30 days after last dose	Every 12 weeks[y]
	Assessments									
				(usually at the next tumor assessment time point).[m]						
NS	CT or MRI of the brain[n]	X		For subjects with previously treated eligible brain metastases, brain scan must be performed at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm immune related-complete response (irCR) within 1 week of response confirmation, or if clinically indicated.					X (unless done within 4 weeks)	X
NS	Bone scan[o]	X		Bone scans (except for subjects with HNSCC) will be performed at screening, every 24 weeks, or sooner if clinically indicated, and at confirmation of irCR.						
S	Archival tumor block or slides[p, s]	X[p]								
S	Fresh Tumor Biopsies (additional consent required) [q]		X[q]				X[q]			
NS	Blood sample for biomarkers[r]		X			X	X		X	

Table 8 Phase 1b: Determination of the Maximum Tolerated Dose: Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

CRF	Phase	Pretreatment		Treatment			Extension			
	Period	**Screening[a,b]**	**Baseline[a,b]**	**Treatment (Cycle 1[b])**			**Treatment (Cycle 2[b] & Beyond)**		**Follow-Up Period[bb]**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**Off-Treatment Visit[u]**	**Follow-up Visits (Off-Tx Visit + 1 day & Beyond)**
	Day	-28 to -3	-3 to -1	1	8	15	1	15	+30 days after last dose	Every 12 weeks[y]
	Assessments									
NS	Blood sample for cf-nucleic acid[r]		X			X	X		X	
NS	Phone Contact[h]				X					
S	Concomitant medications[t]	Throughout								X
S	AEs/SAEs[t]	Throughout								
S	Survival[v]	Throughout								

^{18}F-NaF-PET = 18F Sodium Fluoride (NaF) PET; AE = adverse event, BP = blood pressure, cf-nucleic acid = circulating free nucleic acid, C = cycle, CT = computerized tomography, CRF = case report form, EC = endometrial carcinoma, D = day, ECOG PS = Eastern Cooperative Oncology Group Performance Status, HNSCC = squamous cell carcinoma of head and neck, irCR = immune-related complete response, irPR = immune-related partial response, irRECIST = immune-related Response Evaluation Criteria in Solid Tumors, KPS = Karnofsky performance status, LVEF = left ventricular ejection fraction, M = melanoma, MUGA = multigated acquisition, MRI = magnetic resonance imaging, NSCLC = non-small cell lung cancer, NYHA = New York Heart Association, PD = disease progression or progressive disease, PET = positron emission tomography, PK = pharmacokinetics, pTNM = pathological tumor-node-metastasis, RCC = renal cell carcinoma, RR = respiratory rate, SAE = serious adverse event, UC = urothelial carcinoma, w/in = within.

a. The screening period extends from Day -28 to Day -3. Subjects must be screened within 28 days prior to C1/D1. The screening assessment can serve as the baseline assessment, if performed within 72 h before C1/D1. The baseline assessment can be performed from Day -3 to C1/D1 (prior to the first dose of study drug). Informed consent may be obtained 8 weeks prior to the start of study drug. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit.

b. Efforts should be made to conduct study visits on the day scheduled (±3 days). Treatment cycles will be counted continuously regardless of dose interruptions. Clinical laboratory assessments may be conducted anytime within 72 h prior to the scheduled visit, unless otherwise specified.

c. ECOG PS will be evaluated at the Screening and Baseline Visits, on C2D1, and on Day 1 at every subsequent cycle thereafter. NYHA will only be assessed at the Screening Visit. ECOG and NYHA assessment guidelines are provided in the Appendix of the protocol. Karnofsky performance status will only be assessed for RCC cohort subjects (in addition to ECOG PS) and only at Screening. The KPS scale is provided in the Appendix 8 of the protocol.
d. Assessments will include vital signs (resting BP, HR, RR, and body temperature), weight, and height. Height will be measured at the Screening Visit only. Elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) should be confirmed by 2 assessments 1 hour apart. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. If systolic BP is ≥160 mmHg or diastolic BP is ≥100 mmHg, BP should be confirmed by repeat measurements after an hour. As of Amendment 09, weight and body temperature will be assessed as clinically indicated in the Extension Phase.
e. A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visit, on C1D15, on D1 of each subsequent cycle, and at the Off-Tx Visit assessment. A symptom-directed physical examination will be performed on C1D1 and at any time during the study as clinically indicated. As of Amendment 09, including oral examination.
f. Required if screening physical examination was performed >7 days prior to C1Day 1.
g. Single, 12-lead ECG. Subjects must be in the recumbent position for a period of 5 min prior to the ECG. During the Treatment Phase, ECGs will be collected on Day 1 of every cycle.
h. Phone contact will take place on Day 8 (±2 days) of C1 to assess subjects for development of early toxicity. An unscheduled visit will occur prior to C1D15 if deemed necessary by the investigator
i. Clinical laboratory tests will be performed by the local laboratory. Assessments should be performed within 72 h prior to the visit. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 48 hours after receiving quick estimation. If there is ≥ Grade 3 clinically significant hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 7 days (until improvement to < Grade 3). Thyroid function will be assessed every 2 cycles (C3D1, C5D1, etc.).
j. Urinalysis will be performed at Screening, Baseline, C1D15, and each study visit of every cycle thereafter. Urinalysis will include glucose, hemoglobin (or blood), ketones, pH, protein, specific gravity. If urinalysis suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity test should be performed at the institution's laboratory. If urine protein is ≥2+ on urinalysis, then see Footnote W.
k. A serum and/or urine pregnancy test will be performed at the Screening Visit and the Baseline Visit in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months).
l. Study Treatment PK blood samples drawn 0.5-4 hours, and 6-10 hours post lenvatinib dose on C1D1, prior to dose and 0.5-4 hours, and 6-10 hours post lenvatinib dose on C1D15, and prior to pembrolizumab dose and 2-12 hours post lenvatinib dose on C2D1. Study Treatment PK blood samples drawn prior to pembrolizumab dose only on Day 1 of Cycles 3, 4, 5, and 6.
m. Screening tumor assessments using CT of the chest, abdomen, and pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Subjects with HNSCC must also have scans performed of the head and neck. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast. Treatment Phase: tumor assessments of the (head, neck), chest, abdomen, and pelvis, and other areas where scans were performed at screening or for newly suspected disease should be performed as indicated in the Schedule of Procedures/Assessments above (or sooner if there is evidence of PD) and should use the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments. Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point). Suspected PD must also be confirmed at least 4 weeks after the imaging that initially indicated progression. As of Amendment 09 in the Treatment Period of the Extension Phase, tumor assessments will be performed as per local standard of care but not less frequent than every 6 months As of Amendment 09 in the Follow-Up Period of Extension Phase, tumor assessments will not be collected.
n. Screening brain scans will be performed by MRI pre- and post- gadolinium or CT with contrast within 4 weeks prior to C1D1. During the Treatment Phase, CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves an irCR. For subjects with a history of treated brain metastases, brain scans will be performed at every tumor assessment time point. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability. As of Amendment 09 in the Treatment Period of the Extension Phase, tumor assessments will be performed as per local standard of care but not less frequent than every 6 months. As of Amendment 09 in the Follow-Up Period of Extension Phase, tumor assessments will not be collected.

o. A bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases will be performed within 6 weeks prior to C1D1 (historical scans are acceptable) and then every 24 weeks (within that 24th week) from C1D1 for all tumor types except for HNSCC, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate irCR has been achieved, except for subjects with HNSCC, a bone scan will be required at confirmation of irCR to exclude new bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging. As of Amendment 09 in the Treatment Period of the Extension Phase, tumor assessments will be performed as per local standard of care but not less frequent than every 6 months. As of Amendment 09 in the Follow-Up Period of Extension Phase, tumor assessments will not be collected

p. An archival tumor tissue sample must be available prior to first dose. If archival tumor tissue sample is not available, please see footnotes.

q. Optional fresh paired tumor biopsies will be collected at the baseline and the beginning of Cycle 2 from consented subjects (additional separate consent required) to examine markers including markers of target engagement, relevant pharmacodynamic biomarkers, and potential markers of response.

r. Collection of blood sample to obtain plasma, serum, or other components to be used for biomarker studies. Samples will be obtained at baseline, C1D15, D1 of all subsequent cycles up to and including C18, and at the off-treatment assessment.

s. Subjects with NSCLC require a newly obtained tumor biopsy for biomarker analysis which must be obtained prior to the first dose. If an archival tumor sample for biomarker analysis is not available from subjects with RCC, EC, UC, M, or HNSCC, then a newly obtained tumor biopsy must be obtained prior to the first dose. If a newly obtained biopsy is required, it is preferred that the biopsy is obtained from a non-target lesion. Subjects must have recovered adequately from the biopsy prior to starting therapy.

t. Concomitant meds are recorded for 30 days after last dose.

u. The off-treatment assessment should occur within 30 days after the final dose of study treatment.

v. Survival data will be collected every 12 weeks until end of Treatment Phase (when subjects move into Extension Phase). All anticancer therapy will be recorded until time of death or termination of survival follow up. As of Amendment 09, the Follow-up Period will consist of the Off-Tx Visit. No further visits will be conducted. The sponsor has decided to terminate survival follow-up for all subjects currently in survival follow-up. Survival follow-up data will no longer be collected after the Off-Treatment Visit and after 30 days from the last dose of study drugs.

w. Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on D15 or more frequently as clinically indicated until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months. If a new event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months.

x. 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 3 consecutive months. 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+

y. As long as the study subject is alive and/or until completion of the primary analysis, unless the subject withdraws consent or the sponsor terminates the study. Subjects will be followed-up every 12 weeks (±1 week) for survival and subsequent anticancer treatments.

z. During the Treatment and Extension Phases, MUGA scans or echocardiograms will be performed to assess LVEF every 24 weeks. As of Amendment 09, MUGA scans or echocardiograms will be performed to assess LVEF as clinically indicated during the Extension Phase.

aa. Patients can receive up to 35 treatments (approximately 2 years) with pembrolizumab.

bb. As of Amendment 09, the Follow-up Period will consist of the Off-Tx Visit. No further visits will be conducted. The sponsor has decided to terminate survival follow-up for all subjects currently in survival follow-up.

Table 9 Phase 2 – Expansion in Selected Tumor Types Safety and Efficacy Cohort(s): Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

Phase	Pretreatment		Treatment Phase					Extension Phase			
Period	**Screening[a,b]**	**Baseline[a,b]**	**Treatment Period (Cycle 1[b])**			**Treatment Period (Cycle 2[b] to 8)**		**Treatment Period (Cycle 9[b] & Beyond)**		**Follow-Up[bb]**	
Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**20, 22, 24, etc.**	**21, 23, 25, etc.**	**Off-Treatment Visit[u]**	**Follow-up Visits (Off-Tx Visit + 1 day & Beyond)**
Day	-28 to -3	-3 to -1	1	8	15	1	15	1	15	Days +30 after last dose	Every 12 weeks[x]
Assessments											
Informed consent	X										
Inclusion/exclusion	X	X									
Demographic data	X										
ECOG PS/NYHA[c]	X	X				X		X		X	
KPS[c]	X										
Medical/surgical history	X	X									
pTNM staging at diagnosis	X										
Prior medications	X										
Vital signs[d]	X	X	X		X	X	X[w]	X	X[w]	X	
Physical examination[e]	X	X[f]			X	X		X		X	
12-lead ECG[g]	X		X			X		X		X	

Table 9 Phase 2 – Expansion in Selected Tumor Types Safety and Efficacy Cohort(s): Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

Phase	Pretreatment		Treatment Phase					Extension Phase			
Period	**Screening[a,b]**	**Baseline[a,b]**	**Treatment Period (Cycle 1[b])**			**Treatment Period (Cycle 2[b] to 8)**		**Treatment Period (Cycle 9[b] & Beyond)**		**Follow-Up[bb]**	
Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**20, 22, 24, etc.**	**21, 23, 25, etc.**	**Off-Treatment Visit[u]**	**Follow-up Visits (Off-Tx Visit + 1 day & Beyond)**
Day	-28 to -3	-3 to -1	1	8	15	1	15	1	15	Days +30 after last dose	Every 12 weeks[x]
Assessments											
MUGA or echocardiogram[y]	X		X								
Clinical chemistry & hematology[i]	X	X			X	X		X		X	
Thyroid function test[i]	X	X				X		X		X	
Urinalysis (Dipstick)[j]	X	X			X	X	X[w]	X	X[w]	X	
Pregnancy test[k]	X	X									
Lenvatinib treatment			Throughout								
Pembrolizumab treatment[aa]			X			X		X			
Lenvatinib PK blood samples[l]			X		X	X					
Tumor assessments: CT (MRI)[m]	X		Counting from C1D1, for the first 24 weeks, during Week 6, 12, 18, and 24 (±1 week), or sooner, if clinically indicated, until documentation of confirmed PD. After 24 weeks, tumor assessments must be							X (unless done within 4 weeks)	X

Table 9 Phase 2 – Expansion in Selected Tumor Types Safety and Efficacy Cohort(s): Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

Phase	Pretreatment		Treatment Phase					Extension Phase			
Period	**Screening[a, b]**	**Baseline[a, b]**	**Treatment Period (Cycle 1[b])**			**Treatment Period (Cycle 2[b] to 8)**		**Treatment Period (Cycle 9[b] & Beyond)**		**Follow-Up[bb]**	
Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**20, 22, 24, etc.**	**21, 23, 25, etc.**	**Off-Treatment Visit[u]**	**Follow-up Visits (Off-Tx Visit + 1 day & Beyond)**
Day	-28 to -3	-3 to -1	1	8	15	1	15	1	15	Days +30 after last dose	Every 12 weeks[x]
Assessments											
			performed every 9 weeks counting from C1D1 (during Week 33, 42, 51, 60, etc.) (±1 week), or sooner if clinically indicated, until documentation of confirmed PD. Responses and PD must be confirmed no less than 4 weeks later (usually at the next tumor assessment time point).								
CT or MRI of the brain[n]	X		A brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at screening to assess potential CNS disease and/or metastases. For subjects with previously treated eligible brain metastases, a brain scan must be performed at all tumor assessment time points. For all subjects, a follow-up brain scans must be performed to confirm irCR within 1 week of response confirmation, or if clinically indicated							X (unless done within 4 weeks)	X

Table 9 Phase 2 – Expansion in Selected Tumor Types Safety and Efficacy Cohort(s): Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

Phase	Pretreatment		Treatment Phase					Extension Phase			
Period	**Screening[a, b]**	**Baseline[a, b]**	**Treatment Period (Cycle 1[b])**			**Treatment Period (Cycle 2[b] to 8)**		**Treatment Period (Cycle 9[b] & Beyond)**		**Follow-Up[bb]**	
Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**20, 22, 24, etc.**	**21, 23, 25, etc.**	**Off-Treatment Visit[u]**	**Follow-up Visits (Off-Tx Visit + 1 day & Beyond)**
Day	-28 to -3	-3 to -1	1	8	15	1	15	1	15	Days +30 after last dose	Every 12 weeks[x]
Assessments											
Bone scan[o]	X		Bone scans (except for subjects with HNSCC) will be performed at Screening, every 24 weeks, or sooner if clinically indicated, and at confirmation of irCR								
Archival tumor block or slides[p, s]	X[p]										
Fresh Tumor Biopsies (additional consent required)[q]		X[q]				X[q]					
Blood sample for biomarkers[r]		X			X	X		X		X	
Blood sample for PBMC/cf-nucleic acid[r]		X			X	X		X		X	
RNA Blood sample for Gene Expression[r]		X			X	X		X		X	
Whole blood sample for PG/PD[z]		X									

Table 9 Phase 2 – Expansion in Selected Tumor Types Safety and Efficacy Cohort(s): Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

Phase	Pretreatment		Treatment Phase					Extension Phase			
Period	**Screening[a,b]**	**Baseline[a,b]**	**Treatment Period (Cycle 1[b])**			**Treatment Period (Cycle 2[b] to 8)**		**Treatment Period (Cycle 9[b] & Beyond)**		**Follow-Up[bb]**	
Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**20, 22, 24, etc.**	**21, 23, 25, etc.**	**Off-Treatment Visit[u]**	**Follow-up Visits (Off-Tx Visit + 1 day & Beyond)**
Day	-28 to -3	-3 to -1	1	8	15	1	15	1	15	Days +30 after last dose	Every 12 weeks[x]
Assessments											
Phone Contact[h]				X							
Concomitant medications[t]	Throughout										X
AEs/SAEs[t]	Throughout										
Survival[v]	Throughout										

[18]F-NaF-PET = 18F Sodium Fluoride (NaF) PET; AE = adverse event, , BP = blood pressure, cf-nucleic acid = circulating free nucleic acid, C = cycle, CNS = central nervous system, CT = computerized tomography, D = day, DNA = deoxyribonucleic acid, EC = endometrial carcinoma, ECOG PS = Eastern Cooperative Oncology Group Performance Status, HNSCC = squamous cell carcinoma of head and neck, irCR = immune-related complete response, irPR = immune-related partial response, irRECIST = immune-related Response Evaluation Criteria in Solid Tumors, KPS = Karnofsky performance status, LVEF = left ventricular ejection fraction, M = melanoma (excluding uveal), MUGA = multigated acquisition, MRI = magnetic resonance imaging, NS = not standard, NSCLC = non-small cell lung cancer, NYHA = New York Heart Association, PBMC = peripheral blood mononuclear cells, PD = disease progression, PET = positron emission tomography, PG = pharmacogenomics, PK = pharmacokinetics, pTNM = pathological tumor-node-metastasis, RCC = renal cell carcinoma (predominantly clear cell), RR = respiratory rate, UC = urothelial carcinoma, S = standard, SAE = serious adverse event, w/in = within.

a. The screening period extends from Day -28 to Day -3. Subjects must be screened within 28 days prior to C1D1. The screening assessment can serve as the baseline assessment, if performed within 72 h before C1D1. The baseline assessment can be performed from Day -3 to C1D1 (prior to the first dose of study drug). Informed

consent may be obtained 8 weeks prior to the start of study drug. The results of all screening assessments and evaluations must be completed and reviewed by the investigator prior to the Baseline Visit.

b. Efforts should be made to conduct study visits on the day scheduled (±3 days). Treatment cycles will be counted continuously regardless of dose interruptions. Clinical laboratory assessments may be conducted anytime within 72 h prior to the scheduled visit, unless otherwise specified.
c. ECOG PS will be evaluated at the Screening and Baseline Visits, on Cycle 2/Day 1, and on Day 1 at every subsequent cycle thereafter. NYHA will only be assessed at the Screening Visit. ECOG and NYHA assessment guidelines are provided in the Appendix of the protocol. Karnofsky performance status will only be assessed for RCC cohort subjects (in addition to ECOG PS) and only at Screening. The KPS scale is provided in the Appendix 8 of the protocol.
d. Assessments will include vital signs (resting BP, HR, RR, and body temperature), weight, and height. Height will be measured at the Screening Visit only. Elevated BP assessment (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) should be confirmed by a repeat assessment after a minimum of 1 hour. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks (on Day 1 and Day 15 or more frequently, as clinically indicated) until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months. If a new event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months. As of Amendment 09, weight and body temperature will be assessed as clinically indicated in the Extension Phase.
e. A physical examination will be performed at the Screening or Baseline Visit, on C1D15, on D1 of each subsequent cycle, and at the Off-Tx Visit assessment. A symptom-directed physical examination will be performed on C1D1 and at any time during the study, as clinically indicated. As of Amendment 09, oral examination will be included
f. Required if screening physical examination was performed >7 days prior to C1D1.
g. Single, 12-lead ECG. Subjects must be in the recumbent position for a period of 5 min prior to the ECG. During the Treatment and Extension Phases, ECGs will be collected every cycle.
h. Phone contact will take place on Day 8 (±2 days) of C1 to assess subjects for development of early toxicity. An unscheduled visit will occur prior to C1D15 if deemed necessary by the investigator.
i. Clinical laboratory tests will be performed by the local laboratory. Assessments should be performed within 72 h prior to the visit. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1 and within 48 hours after receiving quick estimation. If there is ≥ Grade 3 clinical significant hematologic or clinical chemistry toxicity, repeat laboratory test and AEs assessment at least every 7 days (until improvement to < Grade 3). Thyroid function will be assessed every 2 Cycles (C3D1, C5D1, etc.).
j. Urinalysis will be performed at Screening, Baseline, C1D5, and each study visit of every cycle thereafter. Urinalysis will include glucose, hemoglobin (or blood), ketones, pH, protein, specific gravity. If urinalysis suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity test should be performed at the institution's laboratory. If urine protein is ≥2+ on urinalysis, then see Footnote W.
k. A serum and/or urine pregnancy test will be performed at the Screening Visit and the Baseline Visit in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months).
l. Study Treatment PK blood samples drawn 0.5-4 hours, and 6-10 hours post lenvatinib dose on C1D1, prior to dose and 0.5-4 hours, and 6-10 hours post lenvatinib dose on C1D15, and prior to pembrolizumab dose and 2-12 hours post lenvatinib dose on C2D1. Study treatment PK blood samples drawn predose only on D1 of Cycles 3, 4, 5, and 6.
m. Screening tumor assessments using CT of the neck/chest/abdomen/pelvis and other areas of known disease or newly suspected disease should be performed within 28 days prior to C1D1. Subjects with HNSCC must also have scans performed of the head and neck. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest should be done with CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast. Treatment Phase: tumor assessments of the (head, neck)/chest/abdomen/pelvis and other areas of known disease at screening or newly suspected disease should be performed as indicated in the Schedule of Assessments/Procedures above during the Treatment Phase (or sooner if there is evidence of PD) and should use the same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments. Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point). Suspected PD must also be confirmed at least 4 weeks after the imaging that initially indicated progression. As of

Amendment 09 in the Treatment Period of the Extension Phase, tumor assessments will be performed as per local standard of care but not less frequent than every 6 months As of Amendment 09 in the Follow-Up Period of Extension Phase, tumor assessments will not be collected.

n. Screening brain scans will be performed by MRI pre- and post- gadolinium or CT with contrast within 4 weeks prior to C1D1. During the Treatment Phase, CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves an irCR. For subjects with a history of treated brain metastases, brain scans will be performed at every tumor assessment time point. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability. As of Amendment 09 in the Treatment Period of the Extension Phase, tumor assessments will be performed as per local standard of care but not less frequent than every 6 months. As of Amendment 09 in the Follow-Up Period of Extension Phase, tumor assessments will not be collected

o. A bone scan (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases will be performed within 6 weeks prior to C1D1 (historical scans are acceptable) and then every 24 weeks within that 24th week) from C1D1 for all tumor types except for HNSCC, or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate CR has been achieved, except for subjects with HNSCC, a bone scan will be required at confirmation of irCR to exclude new bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. Lesions detected on bone scans must be followed with cross-sectional imaging. As of Amendment 09 in the Treatment Period of the Extension Phase, tumor assessments will be performed as per local standard of care but not less frequent than every 6 months. As of Amendment 09 in the Follow-Up Period of Extension Phase, tumor assessments will not be collected

p. An archival tumor tissue sample must be available prior to first dose. If archival tumor tissue sample is not available, please see footnote s.

q. Optional fresh paired tumor biopsies will be collected at the baseline and the beginning of C2 from consented subjects (additional separate consent required) to examine markers including markers of target engagement, relevant pharmacodynamic biomarkers, and potential markers of response.

r. Collection of blood sample to obtain plasma, serum, nucleic acid, or other components to be used for biomarker studies. Samples will be obtained at baseline, C1D15, D1 of all subsequent cycles up to and including C18, and at the off-treatment assessment.

s. For subjects with NSCLC, every effort is to be made to obtain a newly obtained tumor biopsy for biomarker analysis which must be obtained prior to the first dose. If an archival tumor sample for biomarker analysis is not available from subjects with RCC, EC, UC, M, or HNSCC, then a newly obtained tumor biopsy must be obtained prior to the first dose. If a new biopsy is obtained, it is preferred that the biopsy is obtained from a non-target lesion. Subjects must have recovered adequately from the biopsy prior to starting therapy.

t. Concomitant meds are recorded for 30 days after last dose.

u. The off-treatment assessment should occur within 30 days after the final dose of study treatment.

v. Survival data will be collected every 12 weeks until end of the Treatment Phase (when subjects move into Extension Phase). All anticancer therapy will be recorded until time of death or termination of survival follow up. As of Amendment 09, the Follow-up Period will consist of the Off-Tx Visit. No further visits will be conducted. The sponsor has decided to terminate survival follow-up for all subjects currently in survival follow-up. Survival follow-up data will no longer be collected after the Off-Tx Visit and after 30 days from the last dose of study drugs.

w. Urine dipstick testing for subjects with proteinuria ≥2+ should be performed locally on D15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months. Urine dipstick testing should be performed preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site). If a new event of proteinuria ≥2+ occurs, the subject must resume the D15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months. For subjects with a history of dipstick proteinuria ≥2+, see Section 9.4.1.1.3 for management of proteinuria.

x. As long as the study subject is alive and/or until completion of the primary analysis, unless the subject withdraws consent or the sponsor terminates the study. Subjects will be followed every 12 weeks (±1 week) for survival and subsequent anticancer treatments.

y. During the Treatment and Extension Phases, MUGA scans or echocardiograms will be performed to assess LVEF every 24 Weeks. As of Amendment 09, MUGA scans or echocardiograms will be performed to assess LVEF as clinically indicated during Extension Phase.

z. Collection of whole blood to obtain genomic DNA for PG/PD analysis will be obtained during baseline. If sampling is not performed during baseline, sampling may occur at any subsequent visit in which other blood sampling is scheduled to occur.

aa. Patients can receive up to 35 treatments (approximately 2 years) with pembrolizumab.

bb. As of Amendment 09, the Follow-up Period will consist of the Off-Tx Visit. No further visits will be conducted. The sponsor has decided to terminate survival follow-up for all subjects currently in survival follow-up.

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 8 (for Phase 1b) and Table 9 (for Phase 2) for the description and timing of each procedure and assessment in the Pretreatment and Treatment Phase and the Extension Phase, respectively.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies involving subjects with solid tumors.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, 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 the date the investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 24 hours by emailing or faxing the completed SAE form.

Serious adverse events, regardless of causality assessment, must be collected through 90 days after the subject's last dose, or 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. 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.

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

Eisai will provide a Safety Reporting Plan (SRP) for lenvatinib and pembrolizumab. The plan will address the following:

- Holder of the Global Safety Database
- Procedures and timelines for the processing of SAEs
- The distribution of expedited SAE reports
- Responsibility for submission to Health Authorities and notifications to investigators and the EC/IRB
- Adverse Events of Special Interest reports including pregnancy reports, and overdose
- Case closure
- SAE reconciliation
- Translation of source documents
- Schematic of work flow and timelines

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.

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 date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study

9.5.4.3 Reporting of Events Associated with Special Situations

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

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

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

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

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 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 8 and Table 9).

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

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

For Phase 1b study, subjects who discontinue study treatment prior to completing the Treatment Phase for any reason other than a DLT will be replaced. Subjects who discontinue study treatment prior to completing the Phase 2 Treatment Phase for reasons such as lost to follow-up, subject choice, withdrawal of consent, and pregnancy may be replaced.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

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

9.6 Data Quality Assurance

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

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs 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 CCGs. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

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

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

Primary Efficacy Endpoint for Phase 1b:

The primary objective of Phase 1b is to determine the DLTs, MTD, and to establish the RP2D. The efficacy endpoints in Phase 1b will be summarized and listed by dose level based on the Safety Analysis Set. No statistical comparison will be performed.

Primary Efficacy Endpoint for Phase 2:

The primary objective of Phase 2 is to evaluate $ORR_{(Week\ 24)}$ in each of the cohorts using irRECIST. $ORR_{(Week\ 24)}$ is defined as the proportion of subjects who have best overall response (BOR) of $irCR_{(Week\ 24)}$ or $irPR_{(Week\ 24)}$ as of the Week 24 tumor assessment time point. The primary efficacy analysis for each cohort will be performed when all subjects in that cohort have completed 8 cycles of treatment, discontinued due to disease progression, developed unacceptable toxicity, withdrew consent, or the study is terminated by the sponsor.

9.7.1.1.2 SECONDARY ENDPOINTS (BOTH PHASE 1B AND PHASE 2)

The secondary efficacy endpoints will be ORR, PFS, OS, DCR, CBR, DOR, and durable SD rate (SD ≥23 weeks) by irRECIST as appropriate. The secondary efficacy endpoints are defined as follows.

- **ORR** is defined as the proportion of subjects who have BOR of irCR or irPR at the time of data cutoff.
- **PFS** is defined as the time from the first study dose date to the date of first documentation of confirmed disease progression or death (whichever occurs first). If a subject has not experienced disease progression or death, then the subject's data will be censored at the date of the last available tumor assessment.
- **OS** is measured from the start date of the treatment period until date of death from any cause. Subjects who are lost to follow-up and the subjects who are alive at the date of data cutoff will be censored at the date the subject was last known alive.
- **DCR** is defined as the proportion of subjects who have BOR of irCR or irPR or irSD (duration of irSD ≥5 weeks).
- **CBR** is defined as the proportion of subjects who have BOR of irCR or irPR or durable irSD (duration of irSD ≥23 weeks).
- **DOR** is defined as the time from the date the criteria are met for an irCR or irPR (whichever is recorded first) to the date the disease progression is objectively

documented. If a subject has no record of disease progression, then the subject's data will be censored at the last available tumor assessment.

- **Durable SD rate** is defined as the proportion of subjects whose BOR is irSD and the duration of irSD is ≥23weeks.

Determination of the plasma PK profile of lenvatinib while subjects are receiving combination therapy also is a secondary endpoint.

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints include:

- Tumor response endpoints based on investigator assessment using modified RECIST 1.1
- Tumor response endpoints for the subjects in the endometrial and renal cell carcinoma analysis sets based on IIR assessments using irRECIST, modified RECIST 1.1, and RECIST v1.1
- To identify and explore blood and tumor biomarkers which correlate with clinical endpoints of this study including safety and efficacy

9.7.1.2 Definitions of Analysis Sets

Safety Analysis Set will include all subjects who received any amount of study drug. This will be the analysis set for all safety evaluations.

MTD Analysis Set will include all subjects who have completed C1 treatment of Phase 1b or discontinued early due to DLT. This will be the analysis set to determine MTD.

Full Analysis Set (Intent-to-Treat [ITT] Analysis Set) will include all subjects who entered the study treatment period. Efficacy analyses will primarily be based on the Full Analysis Set.

PK Analysis Set All the subjects who have received at least one dose of study drug (lenvatinib) and have evaluable concentration data.

Pharmacodynamic Analysis Set will include all subjects who have received at least one dose of study drug (lenvatinib or pembrolizumab) and have evaluable pharmacodynamic data.

Endometrial Carcinoma Analysis Set will include all EC subjects from Phase 1b and Phase 2.

Renal Cell Carcinoma Analysis Set will include all renal cell carcinoma subjects from Phase 1b and Phase 2.

Non-Small Cell Lung Cancer Analysis Set will include all NSCLC subjects from Phase 1b and Phase 2.

Melanoma Analysis Set will include all melanoma subjects from Phase 1b and Phase 2.

9.7.1.3 Subject Disposition

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

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS will be summarized for each treatment cohort and all treatment cohorts combined using descriptive statistics. Continuous demographic and baseline variables include age, sex, race, region, ECOG-PS, NYHA cardiac disease classification, and pTNM staging.

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 drug codes. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

All efficacy analyses that are conducted at the end of the Treatment Phase will be based on the Full Analysis Set. Selected efficacy analyses may be performed if needed for subjects with the combination of lenvatinib and pembrolizumab as the first line treatment versus other subjects with prior systemic therapies. For the renal cell carcinoma cohort, efficacy subgroup analyses may be presented for treatment naïve subjects, subjects who were previously treated with an anti-PD-1/PD-L1 therapy, and subjects who were previously treated without an anti-PD-1/PD-L1 therapy.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy endpoint in Phase 2 is $ORR_{(Week\ 24)}$ based on irRECIST. Estimated $ORR_{(Week\ 24)}$ and the exact 95% (CI) using the method of Clopper–Pearson will be presented. The primary efficacy analysis of each cohort will be performed when all subjects in that cohort have completed 8 cycles of treatment, discontinued due to disease progression, developed unacceptable toxicity, subject choice, withdrew consent, lost to follow up or the study is terminated by the sponsor.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The following secondary efficacy analyses will be performed on the data collected from the

Phase 2 portion of the study for each treatment cohort.

ORR: ORR and corresponding 95% CI based on exact binomial distribution will estimated for each treatment cohort.

PFS: The distribution of PFS will be estimated using Kaplan–Meier methodology. Median time to PFS and 95% CI will be provided for each treatment cohort. Three-month, 6-month, 9-month, and 1-year PFS rate will be estimated using the Kaplan–Meier method and corresponding 95% CIs will be provided.

OS (overall survival): All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has no record of death, then the data will be censored at the date the subject was last known to be alive, or the data cutoff date, whichever is earlier. The distribution of OS will be estimated using Kaplan–Meier methodology. Median survival time and the corresponding 95% CI, survival rates at 12, 18, and 24 months, and corresponding 95% CIs will be estimated using Kaplan–Meier method for each treatment cohort.

DCR: Disease control rate and exact 95% CI will be estimated for each treatment cohort.

CBR: Clinical benefit rate and exact 95% CI will be estimated for each treatment cohort.

DOR: The distribution of the duration of response will be estimated using Kaplan–Meier Methodology. Median DOR and 95% CI will be provided for each treatment cohort.

Durable SD rate: DSDR and exact 95% CI will be estimated for each treatment cohort.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

The tumor response endpoints will be explored based on modified RECIST 1.1 assessments, and will be summarized and listed by cohort. No statistical comparison will be performed between irRECIST and modified RECIST 1.1 results.

The tumor response endpoints will also be evaluated for the subject in the endometrial and renal cell carcinoma analysis sets using IIR assessment using irRECIST, modified RECIST 1.1, and RECIST v1.1 as exploratory analyses. A concordance analysis will be performed comparing IIR and investigator assessments.

Blood and tumor biomarkers which correlate with efficacy endpoints will be explored.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

To assess any drug–drug interaction between lenvatinib and pembrolizumab, the dose-normalized PK profile for lenvatinib in combination with pembrolizumab from this study

will be compared graphically to that from patients with different tumor types from completed studies receiving lenvatinib monotherapy.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The effect of lenvatinib-pembrolizumab combination therapy on soluble, tissue, genetic and/or imaging biomarkers will be summarized using descriptive statistics using the pharmacodynamic analysis set.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment cohorts, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, and echocardiogram results, including LVEF. Study D1 will be defined as the date of administration of the first dose of study drug.

Selected safety analyses may be performed if needed for subjects with the combination of lenvatinib and pembrolizumab as the first line treatment versus other subjects with prior systemic therapies. For the renal cell carcinoma cohort, safety subgroup analyses may be presented for treatment naïve subjects, subjects who were previously treated with an anti-PD-1/PD-L1 therapy, and subjects who were previously treated without an anti-PD-1/PD-L1 therapy.

9.7.1.8.1 EXTENT OF EXPOSURE

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

9.7.1.8.2 ADVERSE EVENTS

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 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 cohort. 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 highest CTCAE grade.

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

Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by highest CTCAE grade*)*.

Adverse events will be summarized using the Safety Analysis Set. The number of AEs and number and incidence (%) of subjects with AEs will be summarized by cohort/dose level and overall. To obtain the incidence (%), the number of subjects with at least 1 event and the percentage of subjects with AEs by SOC and by PT will be calculated. Incidence (%) by causal relationship with study drug and by severity (CTCAE v4.03) will also be calculated. For clinically significant events, time of onset and recovery will be reported.

Adverse events will be summarized by the following subgroups: age (≤65 years, >65 years), sex (male, female), and race (white, black, other) if necessary.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each cohort. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT for each cohort. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each cohort. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment will be summarized by visit and treatment using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3

will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to the end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory parameters will be categorized according to CTCAE v4.03 grades, and shifts from baseline CTCAE grades to maximum and final postbaseline grades will be assessed. CTCAE 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 visit and overall and by treatment group.

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 cohort.

9.7.1.8.5 ELECTROCARDIOGRAMS

Change from baseline to each postbaseline visit and to the end of treatment in ECG findings (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) will be summarized by visit and treatment group using shift tables. Descriptive statistics for ECG parameters and changes from baseline will be presented by treatment cohort.

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 cohort.

9.7.1.9 Extension Phase Analyses

The Extension Phase data will be analyzed separately and described in the SAP.

9.7.2 Determination of Sample Size

Phase 1b – Determination of the Maximum Tolerated Dose

The total number of subjects required for the Phase 1b portion of this study will depend upon the toxicities observed as the study progresses. A sample size of approximately 10 to 30 subjects in Phase 1b will be enrolled to assess MTD. This is not based on statistical power considerations.

Phase 2 – Expansion in Selected Tumor Types

A sample size of 10 evaluable subjects will be enrolled per cohort, with the possibility of expansion to 20 evaluable subjects per cohort, depending on the evaluation by the sponsor and investigators of the efficacy and safety results observed with the initial 10 evaluable

subjects in each cohort. For a reference of the precision of ORR estimates in all cohorts except the EC and the renal cell carcinoma cohorts, the associated 2-sided 95% CIs for the ORR of 10% to 90% for both 10 subjects and 20 subjects, per cohort are provided in Table 10.

The EC cohort may be further expanded to approximately 120 evaluable subjects. The decision to expand enrollment will be based on the results of 2 interim analyses which will spend β=0.012 and β = 0.024 at the first and second interim analysis, respectively. Based on an assumption of H_0: 16% ORR and H_1: 34% ORR, at 2-sided α = 0.02, this design will give 97% statistical power with 120 subjects. At the first interim analysis (N = 21), if there are more than 3 responses, then approximately 40 additional subjects will be enrolled. At the second interim analysis (N = 60), if there are more than 12 responses, approximately 60 additional subjects will be enrolled. If there are 12 or fewer responses, the sponsor may decide whether to expand enrollment based on clinical outcome, eg, ORR and DOR. If the expansion beyond 60 subjects does not happen, this design for the EC cohort has approximately 86% power at 2-sided α= 0.02. The boundaries for the decision to expand enrollment in the endometrial cohort are presented in Table 11.

Table 10 2-sided 95% Confidence Interval for the ORR of 10% to 90% (10 subjects and 20 subjects)

ORR (N=10)	95% CI
10%	(0.003, 0.445)
20%	(0.025, 0.556)
30%	(0.067, 0.653)
40%	(0.122, 0.738)
50%	(0.187, 0.813)
60%	(0.262, 0.878)
70%	(0.348, 0.933)
80%	(0.444, 0.975)
90%	(0.555, 0.998)
ORR (N=20)	**95% CI**
10%	(0.012, 0.317)
20%	(0.057, 0.437)
30%	(0.119, 0.543)
40%	(0.191, 0.639)
50%	(0.272, 0.728)
60%	(0.361, 0.809)
70%	(0.457, 0.881)
80%	(0.563, 0.943)

Table 10 2-sided 95% Confidence Interval for the ORR of 10% to 90% (10 subjects and 20 subjects)

90%	(0.683, 0.988)

CI = confidence interval, ORR = objective response rate.

Table 11 Boundaries for the Decision to Expand Enrollment in the Endometrial Carcinoma Cohort

Analysis Number	Cumulative β Spent	Objective Response Rate	P-value
Interim Analysis 1 (N=21)	0.012	0.167	0.93
Interim Analysis 2 (N=60)	0.024	0.204	0.357
Final Analysis (N=120)	0.03	0.238	0.02

As of Amendment 7, the renal cell carcinoma cohort may be further expanded to approximately 145 total evaluable subjects to allow for approximately 100 evaluable subjects who have received 1 or 2 prior therapies that included an anti-PD-1/PD-L1 mAb. The decision to expand enrollment will be based on the results of 2 interim analyses. The first interim analysis will take place when 22 subjects (11 treatment naïve and 11 previously treated without an anti-PD-1/PD-L1 mAb) have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 22), if there are more than 5 responses, then approximately 45 additional subjects will be enrolled. It is anticipated that the additional 45 subjects will consist of approximately 12 treatment naïve subjects enrolled under Amendment 05 and approximately 33 previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 mAb. The second interim analysis will include these 45 additional subjects and the 11 treatment naïve subjects included in the first interim analysis and will take place when these 56 subjects have sufficient follow-up to be evaluated for response. Table 12 shows the ORR estimates that are close to the minimum anticipated ORR of about 25% in subjects who had previously failed an anti-PD-1/PD-L1 treatment and about 60% in treatment naïve subjects, and the corresponding 95% CIs in the respective anticipated 33 and 23 subjects for the second interim analysis. At the second interim analysis, whether the previously treated renal cell carcinoma subset will be further expanded will be decided based on clinical review of both efficacy and safety data.

Table 12 Estimate and 2-sided 95% Confidence Interval of the ORR (RCC Subjects for the Second Interim Analysis)

33 subjects who had previously failed an anti-PD-1/PD-L1 therapy		
Number of responses	**Observed ORR**	**95% CI**
7	21.2%	(0.090, 0.389)
8	24.2%	(0.111, 0.423)
9	27.3%	(0.133, 0.455)
10	30.3%	(0.156, 0.487)
11	33.3%	(0.180, 0.518)
12	36.4%	(0.204, 0.549)
23 treatment naïve subjects		
Number of responses	**Observed ORR**	**95% CI**
13	56.5%	(0.345, 0.768)
14	60.9%	(0.385, 0.803)
15	65.2%	(0.427, 0.836)
16	69.6%	(0.471, 0.868)
17	73.9%	(0.516, 0.898)

CI = confidence interval, ORR = objective response rate, PD-1 = programmed cell death protein, PD-L1 = PD-1 ligand, RCC = renal cell carcinoma.

Table 13 shows the 95% CI for a range of observed ORRs from 25% to 45% in subjects who had previously failed an anti-PD-1/PD-L1 treatment with a sample size of 100 subjects. If the observed ORR is 35%, the sample size of 100 subjects will provide a 95% confidence interval with a lower bound excluding 25%, and this indicates that with 95% confidence the ORR in the combination of lenvatinib and pembrolizumab is greater than 25%.

Table 13 Two-sided 95% Confidence Interval of the ORR, N=100 (RCC Subjects Previously Treated with an Anti-PD-1/PD-L1 mAb)

100 subjects who had previously failed an anti-PD-1/PD-L1 therapy		
Number of responses	**Observed ORR**	**95% CI**
25	25.0%	(0.169, 0.347)
30	30.0%	(0.212, 0.400)
35	35.0%	(0.257, 0.452)

40	40.0%	(0.303, 0.503)
45	45.0%	(0.350, 0.553)

CI = confidence interval, mAb = monoclonal antibody, ORR = objective response rate, PD-1 = programmed cell death protein, PD-L1 = PD-1 ligand, RCC = renal cell carcinoma.

9.7.3 Interim Analysis

The evaluation of efficacy and safety by the sponsor and investigators will occur on the initial 10 evaluable subjects while enrollment is ongoing. Based on the outcome of the evaluation the enrollment could be suspended before enrolling the planned 20 subjects in each cohort.

The EC cohort may be expanded to approximately 120 evaluable subjects. Two interim analyses will take place when 21 and 60 subjects have sufficient follow-up to be evaluated for response. The decision to expand enrollment will be based on the results of the 2 interim analyses, which will spend $\beta = 0.012$ and $\beta = 0.024$ at the first and second interim analyses, respectively. Based on an assumption of H_0: 16% ORR and H_1: 34% ORR, at 2-sided $\alpha = 0.02$, this design will give 97% statistical power with 120 subjects. At the first interim analysis (N = 21), if there are more than 3 responses, then approximately 40 additional subjects will be enrolled. At the second interim analysis (N = 60), if there are more than 12 responses, approximately 60 additional subjects will be enrolled. If there are 12 or fewer responses, the sponsor may decide whether to expand enrollment based on clinical outcome, eg, ORR and DOR. If the expansion beyond 60 subjects does not happen, this design for the EC cohort has approximately 86% power at 2-sided $\alpha = 0.02$.

The renal cell carcinoma cohort may be further expanded to approximately 145 evaluable total RCC subjects to allow for approximately 100 evaluable subjects who have received 1 or 2 prior therapies that included an anti-PD-1/PD-L1 mAb. The decision to expand enrollment will be based on the results of 2 interim analyses. The first interim analysis will take place when 22 subjects (11 treatment naïve and 11 previously treated without an anti-PD-1/PD-L1 therapy) have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 22), if there are more than 5 responses, then approximately 45 additional subjects will be enrolled. It is anticipated that the additional 45 subjects will consist of approximately 12 treatment naïve subjects enrolled under Amendment 05 and approximately 33 previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 mAb. The second interim analysis will include these 45 additional subjects and the 11 treatment naïve subjects included in the first interim analysis and will take place when these 56 subjects have sufficient follow-up to be evaluated for response. At the second interim analysis, whether the previously treated renal cell carcinoma subset will be further expanded will be decided based on clinical review of both efficacy and safety data.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

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

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/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 drug will be supplied to the PI (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 Immune-related Response Evaluation Criteria in Solid Tumors

Investigators should follow the guidelines provided here which are an adaptation of RECIST 1.1 and irRC. The following guide represents a summary of irRECIST and is meant to help investigators in providing more objective and reproducible immune therapy related tumor response assessments in solid tumors.

The key changes for irRECIST are:

- IrRECIST allows the site to select up to ten (10) target lesions at baseline, five (5) per organ, if clinically relevant via CT/MRI scans or by electronic calipers for skin lesions. The ability to continue treatment, if clinically stable, until repeat imaging scans ≥4 weeks later (in most cases at the next scanning time point 6 weeks later) to confirm immune-relater progressive disease (irPD)

irRECIST Lexicon	
1. Baseline Assessments	
Measurable (Target) lesions	Measurable lesions must be accurately measured in at least one dimension with a minimum size of: • 10 mm in the longest diameter (LDi) by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis (SDi) for nodal lesions • 10 mm in LDi for clinical lesions (must be measured using electronic calipers) • Identify up to 10 lesions, not more than 5 from one organ system. Lymph nodes are considered one organ system • Likely to be reproducible across all time points • Representative of tumor burden • May include lesions in previously irradiated areas ONLY if there is demonstrated progression in that lesion after irradiation • Sum of diameters (SOD) of all target lesions including nodal and non-nodal are reported as baseline SOD, which is used for assessing tumor response at follow-up time points
Bone lesions	Regardless of the imaging modality, blastic bone lesions will **not be** selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.
Cystic and Necrotic Lesions as Target Lesions	Lesions that are partially cystic or necrotic can be selected as target lesions. The LDi of such a lesion will be added to the SOD of all target lesions at baseline. If other lesions with a nonliquid/nonnecrotic component are present, those should be preferred.

Lesions with Prior Local Treatment	During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (eg, previous irradiation, RF-ablation, TACE, surgery). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progression in the lesion.
Nonmeasurable (Nontarget) lesions	Nontarget lesions will include: • Measurable lesions not selected as target lesions. There is no limit to the number of nontarget lesions that can be recorded at baseline • Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, etc. • Multiple non target lesions from the same organ may be captured as a single item on the eCRF (eg, multiple liver metastases) Nontarget lesions should be reported as present at baseline
SOD $_{\text{baseline}}$	Sum of diameters at baseline = LDi of all non-nodal + SDi of all nodal target lesions
2. Time point Assessments After Baseline	
Target lesion measurements	Locate image that optimizes the LDi of the non-nodal target lesion or SDi of target node(s). There is no need to go to an identical slice from baseline. Measure the respective LDi and SDi for all target lesions and calculate time point SOD (SOD $_{\text{timepoint}}$). Special consideration for target lesions: • If target lesion is too small to measure, a default value of 5mm should be entered on eCRF. • If target lesion is 5-10mm, actual diameter should be entered in the eCRF. • If target lesion splits into 2 or more lesion then the LDi of split lesions will be added and entered in place of that lesion. • If two target lesion merged to form one lesion than LDi of one should be entered as “0mm” while the other lesion should have the diameter of the merged lesion.
Nontarget Lesion Assessment	Nontarget lesions are evaluated qualitatively as present, absent, not evaluable (NE) or unequivocal progression. The response of nontarget lesions primarily contributes to the overall response assessments of irCR. Nontarget lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of nontarget lesions alone, even in the presence of stable disease or a partial response in the target lesion is

	indicative of irPD. IrCR is not possible unless all nontarget lesions are absent.
Definition of New Lesion	Any lesion that was not recorded at baseline. There is no minimum size criteria to identify a new lesion and clinical judgment must be used by the PI. • May include a lesion in an anatomical location that was not scanned at baseline (ie, brain) • Should be unequivocal and not due to differences in scanning technique • If equivocal, should be assessed at next time point; if present, irPD is the date the lesion was first seen (not the date confirmed)
3. irRECIST Overall Tumor Assessment	
irCR	• Complete disappearance of all measurable and nonmeasurable lesions (from baseline) and there are no unequivocal new lesions (unconfirmed irCR). • Lymph nodes must decrease to <10 mm in SDi. • Confirmation of response is required ≥4 weeks later, preferably at next time point, to be considered a confirmed irCR.
irPR	• If the **$SOD_{timepoint}$ of TLs decreases by ≥30 % compared to $SOD_{baseline}$** and there are no unequivocal new lesions, and no progression of nontarget disease, it is an irPR (unconfirmed). • Confirmation is required ≥4 weeks later, preferably at next time point, to be considered a confirmed irPR.
irSD	Failure to meet criteria for irCR or irPR in the absence of irPD. • If the sum of the TLs and the status of the nontarget lesions do not reach the criteria to meet irPR or irPD (increase ≥20% and at least 5 mm absolute increase in SOD compared to nadir†) the response is irSD. • **irSD = neither 30% decrease compared to $SOD_{baseline}$ or 20% increase and at least 5 mm absolute change compared to nadir.** • **†SOD_{nadir}:** Lowest measure SOD of TLs at any time point from baseline onward.
irPD	Minimum 20% increase and a minimum 5 mm absolute increase in SOD compared to nadir, or irPD for nontarget lesion(s) or unequivocal new lesion(s). • Confirmation of progression is recommended at a minimum of 4 weeks after the first irPD assessment (preferably at next tumor assessment time point). The decision to continue study treatment after the first evidence of PD is at the investigator's discretion based on the clinical status of the subject as described in table below

<table>
<tr><td></td><td>
<table>
<tr><td></td><td colspan="2">Clinically Stable</td><td colspan="2">Clinically Unstable</td></tr>
<tr><td></td><td>Imaging</td><td>Treatment</td><td>Imaging</td><td>Treatment</td></tr>
<tr><td>1st radiologic evidence of PD</td><td>Repeat imaging at ≥4 weeks (next TA time point) to confirm PD</td><td>May continue study treatment at the Investigator's discretion while awaiting confirmatory scans</td><td>Repeat imaging at ≥4 weeks to confirm PD per physician discretion only</td><td>Discontinue treatment</td></tr>
<tr><td>Subsequent scan confirms PD</td><td>No additional imaging required</td><td>Discontinue treatment</td><td>No additional imaging required</td><td>N/A</td></tr>
<tr><td>Subsequent scan shows SD, PR or CR</td><td>Continue regularly scheduled imaging assessments</td><td>Continue study treatment at the Investigator's discretion</td><td>Continue regularly scheduled imaging assessments</td><td>May restart study treatment if condition has improved and/or clinically stable per investigator's discretion</td></tr>
</table>

Subjects may continue receiving study treatment while waiting for confirmation of irPD if they are clinically stable as defined by the following criteria:
• Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
• No decline in ECOG performance status
• Absence of rapid progression of disease
• Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

If irPD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact sponsor to discuss continuing treatment
</td></tr>
<tr><td>irNE</td><td>Used in exceptional cases where insufficient data exists due to poor quality of scans or missed scans or procedure</td></tr>
</table>

Derivation of irRECIST overall responses

Measurable response	Non-measureable response		
Target Lesions (% change in SOD)[a]	**Nontarget Lesions Status**	**New Lesions Status**	**Overall Response (irRECIST)**
↓100	Absent	Absent	irCR[b]
↓100	Present/NE	Absent	irPR[b]
↓≥30	Present/Absent/NE	Absent	irPR[b]

↓<30 to <20↑	Present/Absent/NE	Absent	irSD
↓100 ↓≥30 ↓<30 to <20↑ NE	Present/Absent/NE	Present	irPD[b]
↓100 ↓≥30 ↓<30 to <20↑ NE	Unequivocal progression	Any	irPD[b]
↑≥20 from nadir	Any	Any	irPD[b]
NE	Present/Absent/NE	Absent	irNE[b]

irCR = immune-related complete response, irNE = immune-related not evaluable, irPD = immune-related progression disease, ir PR = immune-related partial response, irSD = immune-related stable disease, NE = Not evaluable, irRECIST = immune-related Response Evaluation Criteria in Solid Tumors SOD = sum of diameters

a: Decreases assessed relative to baseline, including measureable lesions only.

b: Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Appendix 2 Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

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

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

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

The CTCAE v4.03, published 14 June 2010 provides descriptive terminology to be used for AE reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all AE terms in CTCAE v4.03 have been correlated with single-concept (MedDRA) terms.

The CTCAE v4.03 grading refers to the severity of the AE. The CTCAE 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.meddramsso.com

Appendix 4 New York Heart Association (NYHA) Cardiac Disease Classification

The NYHA 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: Little Brown; 1994. p.253-6.

Appendix 5 Clinical Studies Evaluating Drug–Drug Interactions with Lenvatinib

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

Simultaneous CYP3A4/ 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.

Appendix 6 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic, 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 AEs 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 7 KEYTRUDA® Package Insert

The latest KEYTRUDA Package Insert (Revised: 09/2017) is available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s024lbl.pdf

KEYTRUDA Summary of Product Characteristics (Revised: 10/2017) is available at:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003820/WC500190990.pdf

Appendix 8 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.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E7080-A001-111
Study Protocol Title:	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors
Investigational Product Name:	Lenvatinib (E7080/LENVIMA™) and Pembrolizumab (MK-3475/KEYTRUDA®)
IND Number:	72010
EudraCT Number:	2017-000300-26

SIGNATURES

Authors:

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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-A001-111
Study Protocol Title:	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors
Investigational Product Name:	Lenvatinib (E7080/LENVIMA™) and pembrolizumab (MK-3475/KEYTRUDA®)
IND Number:	72010
EudraCT Number:	2017-000300-26
Study Protocol Number:	E7080-A001-111

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

Medical Institution

Investigator	Signature	Date