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Clinical Study Protocol

Study Protocol Number:	E7080-J081-115
Study Protocol Title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subjects with Selected Solid Tumors
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-ku, Tokyo 112-8088, Japan
Investigational Product Name:	Lenvatinib (E7080/LENVIMA™) and Pembrolizumab (MK-3475/KEYTRUDA®)
Indication:	Solid tumors
Phase:	Phase 1b
Approval Date:	V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendement 01) 10 Apr 2018 (Amendement 02) 05 Apr 2019 (Amendement 03) 14 Feb 2020 (Amendement 04) 07 Apr 2020 (Amendement 05)
GCP Statement:	This study is to be performed in full compliance with Japan's Good Clinical Practice (GCP) and all applicable 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.

Summary of Changes
Revisions to Amendment 05
Date: 07 Apr 2020

Change	Rationale	Affected Protocol Sections
Change **Study Period and Phase of Development**	For extending study period.	• Clinical Protocol synopsis

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080, MK-3475

Name of Active Ingredient: Lenvatinib, Pembrolizumab

Study Protocol Title

An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subjects with Selected Solid Tumors

Study Regions (Country) or Center

One center in Japan

Study Period and Phase of Development

54 months (plan)

Phase 1b

Objectives

Primary Objective

- To confirm the tolerability and safety for combination of lenvatinib plus pembrolizumab in subjects with selected solid tumors

Secondary Objectives

- To evaluate the following efficacy endpoints by Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) and modified RECIST 1.1:
  - Objective response rate (ORR)
  - Duration of response (DOR)
- To assess the pharmacokinetic (PK) profile of lenvatinib and pembrolizumab
- To detect anti-drug antibodies for pembrolizumab (ADA)

Exploratory Objectives

- To evaluate the following efficacy endpoints by irRECIST and modified RECIST 1.1:
  - Progression-free survival (PFS)
  - Time to response (TTR)
  - Disease control rate (DCR)
  - Clinical benefit rate (CBR)
- To investigate the relationship between candidate biomarkers and anti-tumor activity of lenvatinib in combination with pembrolizumab:
  - To explore blood and tumor markers (such as programmed cell death protein 1 ligand 1 [PD-L1] expression levels, cytokine and angiogenic factor profiling), and immune cell profiling and evaluate their relationship with clinical outcomes including anti-tumor activity of lenvatinib in combination with pembrolizumab

Study Design

Overall Design

This is an open-label Phase 1b study. This study will confirm the tolerability and safety of lenvatinib in combination with pembrolizumab in subjects with selected solid tumors. Subjects in

this study will have one of the following tumors: non-small cell lung cancer, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma (excluding uveal melanoma).

This study will begin with lenvatinib 20 mg/day orally and pembrolizumab 200 mg (every 3 weeks [Q3W], intravenous [IV]) in subjects with selected solid tumors on a 21-day treatment cycle. For the confirmation of the tolerability of the dose level, dose limiting toxicities (DLTs) will be evaluated during the first cycle (21 days).

If 0 or 1of 6 subjects in a given dose level cohort experiences a DLT, the dose level will be considered tolerable.

Enrollment will be interrupted if 2 or more DLTs are observed at any dose level, and after sponsor and investigators' review, enrollment may continue for up to 6 subjects based on the nature and severity of the DLTs. Once 6 subjects are enrolled, then, 4 additional subjects (10 subjects in total) will be added and that dose level will be considered tolerable if DLT is observed in 3 or less of the10 subjects in total. An independent medical advisor as third party should be consulted for the review as needed.

A lower dose level of lenvatinib of 14 mg once daily (QD) in combination with 200 mg pembrolizumab Q3W or study discontinuation will be considered, if 20 mg lenvatinib plus 200 mg pembrolizumab dose level is not tolerable, upon discussions between the sponsor and investigators, and the protocol will be amended as necessary. An independent medical advisor as third party should be consulted for the consideration as needed.

If there is a potential subject who is not evaluable for DLT (eg, subject who fails to administer ≥75% of the planned dosage of lenvatinib due to a reason other than treatment related toxicity during Cycle 1), the investigator and sponsor will discuss whether or not to include the subject in the DLT Analysis Set. If subject is not evaluable for DLT then the subject will be replaced.

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 in Cycle 1
- Greater than 2 weeks delay in starting pembrolizumab in 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 1 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 1 hour, with life-threatening consequences and urgent intervention indicated.

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.

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** consists of the first cycle (21 days) for each subject. The Treatment Phase for each subject ends after completing Cycle 1 of treatment or if 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.

Extension Phase

The Extension Phase begins after a subject completes Cycle 1 and ends when the subject completes the Off-Tx Visit. It 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 who discontinue study treatment transition to the Off-Tx Visit of the Follow-up Period of the Extension Phase.

Follow-up Period (Extension Phase): The Follow-up Period consists of the Off-Tx Visit. The Off-Tx Visit will occur within 30 days following the last dose of study treatment.

Number of Subjects

This study will enroll between 6 and 10 evaluable subjects with selected solid tumors.

Inclusion Criteria

1. Histologically and/or cytologically confirmed selected solid tumor types that have progressed after treatment with standard therapies or for which there are no other appropriate 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.

The selected tumor types are: non-small cell lung cancer, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma (excluding uveal melanoma)

2. At least 1 measurable target lesion according to modified RECIST 1.1
3. Subjects must have an Eastern Cooperative Oncology Group (ECOG)-Performance Status (PS) of 0 to 1.
4. 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/Day 1 (C1D1)
5. Adequate renal function defined as creatinine ≤1.5 times the upper limit of normal (ULN) or calculated creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula with creatinine levels >1.5×ULN
6. Adequate bone marrow function:
   - Absolute neutrophil count (ANC) ≥1500/mm^3 (≥$1.5\times10^3/\mu L$)
   - Platelets ≥100,000/mm^3 (≥$100\times10^9/L$)
   - Hemoglobin ≥9.0 g/dL
7. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5
8. Adequate liver function as evidenced by bilirubin ≤1.5×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 must be separated from the total and used to assess the liver function instead of the total ALP.
9. Males or females age ≥20 years at the time of informed consent
10. Life expectancy of 12 weeks or more
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.
12. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol
13. Archival tumor tissue or a newly obtained biopsy must be available prior to the first dose of study drug for biomarker analysis. Subjects 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 28 days prior to the first dose of study drugs. All toxicities related to prior treatments must be resolved to Grade ≤1(except alopecia).
   Note: Refer to inclusion criteria regarding Hypertention.

2. 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.
3. Prior treatment with lenvatinib or any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, excluding cancer types such as melanoma and non-small cell lung cancer where prior treatment with one anti-PD-1, anti-PD-L1, or anti-PD-L2 agent is allowed.
4. Subjects must have recovered adequately from any complications from major surgery prior to starting therapy.
5. Subjects having ≥2+ 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.
6. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib
7. 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
8. Prolongation of QTc (Fridericia formula) interval to >480 ms
9. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug
10. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (eg, carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
11. Active infection (any infection requiring systemic treatment)
12. Subject is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C.
13. Serious nonhealing wound, ulcer, or bone fracture
14. Known intolerance to either of the study drugs (or any of the excipients)
15. History of organ allograft
16. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial
17. 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
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 7.5 mg/d of prednisone or equivalent) may be approved after consultation with the sponsor.
19. 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 [T4], 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, or has a history of interstitial lung disease.
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.
22. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
23. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
24. Females of childbearing potential* who:
    - do not agree to use a highly effective method of contraception for the entire study period and for 120 days after study drug discontinuation ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or hormone releasing system (IUS)
        - a contraceptive implant
        - an oral contraceptive** (with additional barrier method)

    OR

    - do not have a vasectomized partner with confirmed azoospermia.

    For sites outside of the European Union (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 [i.e., 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.
25. 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 Exclusion Criterion #24) 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.

Study Treatments

Lenvatinib

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.

On Day 1 of each cycle, in case concomitantly administered, it will be administered approximately within 1 hour after completion of pembrolizumab administration.

Pembrolizumab

Pembrolizumab will be provided as a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous 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.

Pembrolizumab will be administered until 2 years after C1D1 at the longest.

Study Treatment Dose Modification

1. Cycle 1

a. If DLT occurs:

Lenvatinib and infusion of pembrolizumab should be interrupted immediately. Treatment may be resumed in Cycle 2 of pembrolizumab at the same dose (except the toxicity which requires the permanent discontinuation according to the guidance) and at 1 lower dose level of lenvatinib if toxicity is resolved to Grade 0–1 (or torelable Grade 2 in case of lenvatinib treatment-related toxicity) or baseline and investigators decides to continue the study.

b. No DLT

Lenvatinib will be interrupted if judged to be clinically needed by investigators, and may be resumed at the same dose level at appropriate timing.

2. Cycle 2 and onward

Lenvatinib

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose reduction instructions shown in the tables below for this study, respectively.

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 (4 mg every other day) must be discussed with the sponsor. Once the dose has been reduced, it cannot be increased at a later date.

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		

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

Lenvatinib in Combination with Pembrolizumab Toxicity

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

QD = once daily.
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 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 1 week 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

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 Section 9.4.1.5 for supportive care guidelines, including use of corticosteroids.

Toxicity	Hold Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 Diabetes Mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when subjects are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4 Recurrent 2	Permanently discontinue	Permanently discontinue

Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c, d]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, T1DM = type 1 diabetes mellitus.

a: For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

b: If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Infusion Reaction Treatment Guidelines.

c: Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

d: For asymptomatic Grade ≥3 elevations of amylase and lipase, the sponsor should be consulted to obtain permission to continue treatment.

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 Study

Study duration for each subject is estimated to be:

- **Pretreatment Phase:** 28 days
- **Treatment Phase:** 21 days (Cycle 1)
- **Extension Phase:** Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor termination of the study.

Concomitant Drug/Therapy

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 Pretreatment, Treatment, and Extension Phase of this study:

- Anticancer therapies such as chemotherapy, tyrosine kinase inhibitors (TKIs), antitumor interventions (surgical resection, thoracocentesis, etc.), or immunotherapy

- Investigational agents other than lenvatinib and pembrolizumab
- Radiation therapy
  Note: Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases without being considered progressive disease may be considered on an exceptional 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, 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 clinical interest 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.

Assessments

Efficacy

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. They must be accessible in the event of a sponsor request to submit them for central review.

Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks (±1 week; counting from C1D1) until Week 24, then every 9 weeks (±1 week) during treatment cycles in the Extension Phase. Computed tomography (CT) /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 C1D1), at all tumor assessment time points, and as indicated clinically. Color photographs containing a milimeter 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.

MRI 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 complete response (irCR), or if clinically indicated.

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

Subjects going off treatment without disease progression (excluding the subject with CR at off-treatment visit) 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 (as needed), or sooner if clinically indicated, and at confirmation of irCR. Lesions identified on bone scans must be verified and followed with correlative cross-sectional imaging.

In order for stable disease (irSD) to be considered the best overall response (BOR), 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. Responses (irPR [partial response] 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 progressive disease (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 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 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-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). Responses (PR or CR) should be confirmed no less than 4 weeks after the initial response, but generally at the next scheduled tumor assessment time point. In order for SD to be considered BOR, it must occur ≥5 weeks following the first dose of study drug.

Pharmacokinetic

Plasma concentrations of lenvatinib and serum concentrations of pembrolizumab will be measured. Serum ADA will be also measured.

Pharmacodynamic/Pharmacogenomic

Blood and Tissue Biomarkers: Blood samples for the development of exploratory predictive biomarkers will be collected from consented subjects prior to the first dose of study drug (C1D1), on Cycle 1/Day 15 (C1D15), and on Day 1 of subsequent cycles up to and including Cycle 18, 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 (subjects with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the sponsor). 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 serum 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 consented subjects for potential assessment of mutations and other genetic alterations or genes and/or proteins including PD-1/PD-L1/PD-L2 status and other relevant biomarkers (eg, tumor infiltrating lymphocytes, T-cell repertoire, ribonucleic acid [RNA] signature profiles, mutational load) 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.

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 and investigators judge that it is medically acceptable to have a biopsy).

A blood plasma sample to isolate circulating cell free nucleic acids (cf-nucleic acids) and a whole blood sample for immune cell profiling will be collected from consented subjects prior to the first dose of study drug (C1D1), and then pre-dose on C1D15 and Day 1 of subsequent cycles up to and including Cycle 18 and at the off-treatment assessment. Cf-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. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor and to assess the immune response.

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 adverse events (AEs) and serious adverse events (SAEs), using Common Terminology Criteria for Adverse Events (CTCAE) v4.03; regular laboratory evaluation for hematology, blood chemistry, and urine values; regular performance of physical examinations, periodic measurement of vital signs, and electrocardiograms (ECGs); and echocardiograms or multigated acquisition (MUGA) scans including left ventricular ejection fraction (LVEF).

Bioanalytical Methods

Plasma concentrations of lenvatinib and serum concentrations of pembrolizumab will be measured by using validated methods. Serum ADA will be detected by using validated methods.

Statistical Methods

Study Endpoints

The following endpoints will be defined in 2 ways based on irRECIST and modified RECIST 1.1.

ORR is defined as the proportion of subjects who have BOR of (ir)CR or (ir)PR at the time of data cutoff.

ORR$_{(Week\ 24)}$ is defined as the proportion of subjects who have BOR of (ir)CR$_{(Week\ 24)}$ or (ir)PR$_{(Week\ 24)}$ as of the Week 24 tumor assessment time point.

DOR is defined as the time from the first documentation of (ir)CR or (ir)PR to the date of first documentation of disease progression (based on irRECIST and modified RECIST 1.1) or death (whichever occurs first).

PFS is defined as the time from the first study dose date to the date of first documentation of disease progression (based on irRECIST and modified RECIST 1.1) or death (whichever occurs first).

TTR is defined as the time from the date of first study dose to the date of first documentation of (ir)CR or (ir)PR.

DCR is defined as the proportion of subjects who have BOR of (ir)CR or (ir)PR or (ir)SD (minimum duration from C1D1 to (ir)SD ≥5 weeks).

CBR is defined as the proportion of subjects who have BOR of (ir)CR or (ir)PR or durable (ir)SD (duration of (ir)SD ≥23 weeks).

Analysis Sets

DLT Analysis Set will include all subjects who have completed Cycle 1 without major protocol deviation with at least 75% of study drug compliance and are assessed for DLT, and subjects who have experienced DLT during Cycle 1. This will be the analysis set to confirm tolerability.

Safety Analysis Set/Efficacy Analysis Set will include all subjects who received at least 1 dose of study drug.

PK Analysis Set will include all subjects who have received at least 1 dose of lenvatinib and pembrolizumab, and have evaluable concentration data.

Efficacy Analyses

Efficacy analyses will be based on the Efficacy Analysis Set. BOR will be summarized, and ORR, ORR$_{(Week\ 24)}$, and their corresponding exact 2-sided 95% confidence interval (CI) will be calculated. DOR will also be summarized and plotted over time by Kaplan-Meier method. Likewise, PFS and TTR will be analyzed as needed. If applicable, DCR, CBR, and their corresponding exact 2-sided 95% CI will also be calculated. If applicable, a waterfall plot will be presented for the percent

changes from baseline in the sum of the diameters of target lesions at postbaseline nadir (ie, maximum tumor shrinkage).

Pharmacokinetic and/or Pharmacodynamic Analyses

Pharmacokinetic

The primary PK parameters of lenvatinib under combination will be calculated using noncompartmental analysis and compared with historical data after single dose using the PK analysis set. If warranted, additional analyses may be performed. PK data for lenvatinib and pembrolizumab is planned to be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this study and from other studies, a population PK analysis may be performed to characterize PK parameters to support the proposed dosing regimen. PK data for lenvatinib and pembrolizumab may also be used to explore the exposure-response relationships for antitumor activity/efficacy as well as biomarkers and safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately. For serum ADA levels, a listing of results will be made.

Pharmacodynamic

The effect of lenvatinib-pembrolizumab combination therapy on soluble, tissue, genetic and/or imaging biomarkers will be summarized using descriptive statistics. PK/pharmacodynamic relationships will be explored graphically and may be investigated by model-based analyses. Details of the analysis will be provided in a separate analysis plan. The results of these analyses, if performed, will be reported separately.

Tolerability/Safety Analyses

All tolerability analyses will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated. Safety analyses will be performed on the Safety Analysis Set. The number (percentage) of subjects with treatment-emergent AEs (TEAEs) and treatment-emergent SAEs will be summarized by system organ class (SOC) and preferred term (PT). Summary statistics will be presented for laboratory test values, vital sign, and 12-lead ECG parameters. If needed, the changes from baseline will also be summarized.

Sample Size Rationale

A sample size of 6 to 10 subjects in this study. This is not based on statistical power considerations.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
BOR	best overall response
BP	blood pressure
C#/D#	Cycle#/Day#
CBR	clinical benefit rate
cf-nucleic acid	cell free nucleic acid
CI	confidence interval
CLIA	clinical laboratory improvement amendments
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCR	disease control rate
DKA	diabetic ketoacidosis
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis

Abbreviation	Term
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EU	European Union
FDA	United States Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FGFR	fibroblast growth factor receptor
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HNSCC	squamous cell carcinoma of head and neck
ICF	informed consent form
ICH	International Conference on Harmonisation
IL-10	interleukin 10
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
irRC	immune-related response criteria
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
IxRS	interactive voice/web response system
KIT	a stem cell factor receptor
LC/MS/MS	liquid chromatography with tandem mass spectrometry

Abbreviation	Term
LDi	longest diameter
LLT	lower level term
LMWH	low-molecular-weight heparin
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not evaluable
NSAIDs	nonsteroidal antiinflammatory drugs
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
Off-Tx	off treatment
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PDGFR	platelet-derived growth factor receptor
PD-L1 (or 2)	PD-1 ligand 1 (or 2)
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetics
PO	per os
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PT	preferred term
Q3W	every 3 weeks
QD	once daily
QT	time from the beginning of the QRS complex to the end of the T wave

Abbreviation	Term
QTc	QT interval corrected for heart rate
RP2D	recommended Phase 2 dose
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RET	ret proto-oncogene
RF	radiofrequency
RNA	ribonucleic acid
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SDi	short axis
SI	Système International
SOC	system organ class
SOD	sum of diameter
SOP	standard operating procedure
T1DM	type 1 diabetes mellitus
T4	thyroxine
TACE	transcatheter arterial chemo-embolization
TAM	tumor-associated macrophage
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TGFβ	transforming growth factor, beta 1
TKI	tyrosine kinase inhibitor
t_{max}	time to maximum concentration
TNM	tumor-node-metastasis
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with Japan's Good Clinical Practice (GCP). Any protocol amendment or revision to the ICF will be resubmitted to the IRB 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 compliance with Japan's GCP regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB chairman must be sent to 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. If the IRB decides to suspend or terminate the study, the head of the medical institution will immediately send the notice of study suspension or termination by the IRB to the sponsor.

Study progress is to be reported to IRBs annually (or as required) by the investigator via the head of the medical institution according to Japan's GCP. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the investigator and the relevant IRB via the head of the medical institution of any reportable adverse events (AEs) per Japan's GCP and local IRB standards of practice. Upon completion of the study, the investigator via the head of the medical institution will provide the IRB and the sponsor with a brief report of the outcome of the study.

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki
- Japan's GCP
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceuticals, Medical devices and Other Therapeutic Products Act (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP

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-approved ICF must be prepared in accordance with Japan's GCP 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 pharmacogenomic 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 1 investigational site in Japan. Additional sites will be considered as needed.

The name and telephone and fax numbers of the sponsor's responsible medical officer and other contact personnel at the sponsor are listed in the Attachment 1.

7 INTRODUCTION

The goal of Study E7080-J081-115, which will be conducted in patients, is to confirm the tolerability and safety for combination of lenvatinib plus pembrolizumab in Japanese subjects with selected solid tumors: non-small cell lung cancer, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma (excluding uveal melanoma).

7.1 Indication

7.1.1 Lenvatinib

Vascular endothelial growth factor receptor (VEGFR) is expressed in vascular endothelial cells, playing a vital role for physiological and pathological angiogenesis and lymphogenesis or in the malignant cells led by vascular endothelial growth factor (VEGF) ligand stimulation (Ellis LM, et al., 2008, Ferrara N, et al., 2003, Hattori K, et al., 2002, Laakkonen P, et al., 2007, Tammela T, et al., 2010). Fibroblast growth factor receptor (FGFR), platelet-derived Growth Factor receptor-α (PDGFRα), RET, and KIT are also known to be associated with angiogenesis, proliferation, or both (St Bernard R, et al., 2005, Turner N, et al., 2012, Matsui J, et al., 2004, Hirota S, et al., 1998, Williams D, 2002, Kondo T, et al., 2006, Phay JE, et al., 2010, Gild ML, et al., 2011, Hirota S, et al., 2003, Oseini AM, et al., 2009) and an effective anticancer treatment may be established if their receptor tyrosine kinases (RTKs) are inhibited simultaneously.

Lenvatinib mesylate was developed at Eisai Tsukuba Research Laboratories to explore agents that inhibit RTKs activities associated with tumor angiogenesis. It is a multikinase inhibitor that exhibits potent inhibitory effects not only on VEGFR1 to VEGFR 3 at the level of inhibition constant Ki 1 nmol/L, but also on FGFR 1 to FGFR4 and KITs.

In nonclinical studies, lenvatinib showed inhibitory activities dose-dependently in VEGFR2-driven phosphorylation, tube formation and proliferation in human vascular endothelial cells (human umbilical vein endothelial cell – HUVEC) induced by VEGF. In vivo study where human cancer cells are transplanted in immune deficient mouse models, lenvatinib also demonstrated high anticancer effect in a wide variety of cancers. In addition, safety results in nonclinical studies showed lenvatinib was well tolerated within the therapeutic range.

Three phase 1 studies were conducted in Japan, US, and Europe with different regimen to determine the safety, tolerability, and pharmacokinetics of lenvatinib. Treatment regimen for each study was: continuous once daily for E7080-E044-101 (Europe), continuous twice daily for E7080-A001-102 (US), and twice daily for 2 weeks with dosing intervals of 1 week for E7080-J081-103 (Japan). Based on the results from these studies, a continuous dose of 24 mg once daily has been selected to treat solid tumors for ongoing lenvatinib development. The tolerability in 24 mg once daily continuous dose in Japanese patients was confirmed in another study conducted in Japan (E7080-J081-105). There was no significant difference in tolerability and pharmacokinetics among patients in Japan, Europe, and US.

Lenvatinib is expected to be efficacious regardless of cancer type; clinical studies are being conducted for various solid malignancies including thyroid carcinoma, hepatocellular carcinoma, renal cell carcinoma, non-small-cell lung cancer, endometrial cancer, glioma, malignant melanoma, and ovarian cancer.

Lenvatinib is approved in the US for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, and approved in Japan with an indication for unresectable thyroid cancer.

As outlined below, data from Phase 2 clinical studies showed lenvatinib monotherapy has antitumor activity in multiple other tumors.

In patients with locally advanced or metastatic non-squamous non small cell lung cancer (NSCLC), treated with lenvatinib 24 mg once daily + best supportive care, lenvatinib was found to be active with longer survival in these patients who had had 2 or more lines of prior treatment. Overall survival (OS) was the primary objective of this study (E7080-703).

In a 3 arm study of lenvatinib 24 mg once daily, everolimus 10 mg once daily, and the combination of lenvatinib 18 mg with everolimus 5 mg in patients with unresectable advanced or metastatic renal cell carcinoma (E7080-G000-205), lenvatinib monotherapy showed plonongation of PFS compared with everolimus monotherapy.

In a study (E7080-G000-204) to evaluate the antitumor activity of lenvatinib 24 mg once daily in female patients with surgically unresectable endometrial cancer who have disease progression following 1 prior platinum-based, systemic chemotherapy regimen, the objective response rate (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 patients with advanced endometrial cancer.

A study was conducted to determine the activity of lenvatinib 24 mg once daily in previously treated patients 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 patients with melanoma not harboring the V600E BRAF mutation and 9.0% in patients with melanoma harboring the activating BRAF mutations (mainly the V600E mutation). All were partial responses.

7.1.2 PD-1 Inhibitors and Pembrolizumab

Antitumor immunity is often ineffective due to the tight regulation associated with the maintenance of immune homeostasis (Stagg J, et al., 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 R, et al., 2003). Compelling evidence indicates that B7 proteins can suppress T-cell responses (Chen L, 2004, Sharpe AH, et al., 2002) aiding tumor immune evasion. These negative signals are largely provided by 2 members of the B7-family. One of these is programmed cell death protein 1

(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 tumour microenvironment. Indeed, expression of the PD-1 ligand, PD-L1, has been shown to be associated with poor prognosis in melanoma and hepatocellular carcinoma (Gadiot J, et al., 2011, Gao Q, et al., 2009, Topalian SL, et al., 2012).

Clinically, blockade of PD-1 or PD-L1, using monoclonal antibodies, has demonstrated substantial clinical activity in patients with metastatic melanoma, renal cell carcinoma, NSCLC, bladder, head and neck cancers, and other tumors (Brahmer JR, et al., 2012, Hamid O, et al., 2013, Philips GK, et al., 2015, Robert C, et al., 2014).

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (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 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 brochure.

A pembrolizumab population pharmacokinetic (PK) analysis has been performed using data from 476 subjects. Based on the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has a similar safety and efficacy profile over the range of doses ranging from 2 mg/kg to 10 mg/kg (Robert C, et al., 2014). The differences in exposure for a 200 mg every 3 weeks (Q3W) regimen, the dose proposed for this study, relative to the approved 2 mg/kg Q3W regimen in the US Package Insert (see Appendix) are anticipated to remain well within the established exposure margins of 0.5- to 5.0-fold for pembrolizumab in the melanoma indication. These exposure margins are based on the similar efficacy and safety seen in patients with melanoma at 10 mg/kg Q3W versus the dose regimen of 2 mg/kg Q3W (ie, a 5-fold higher dose and exposure) noted above. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

No dose reduction is allowed for pembrolizumab in this study.

7.2 Combination of Lenvatinib Plus Pembrolizumab

7.2.1 Nonclinical

It is reported that VEGF/VEGFR signal exhibits proangiogenic properties but also has a key role in the induction of an immunosuppressive microenvironment (Gabrilovich DI, et al., 1996, Huang Y, et al., 2007, Terme M, et al., 2013, Voron T, et al., 2015). Therefore, it is expected that lenvatinib which inhibit VEGFR can also have immune modulating activity.

The effect of combining lenvatinib with PD-1/L1 (programmed death, ligand 1) monoclonal antibodies (mAbs) has been investigated in the CT26 murine colorectal cancer syngeneic model (PD-L1 mAb) as well as the LL/2 murine lung cancer syngeneic model (PD-1 mAb). Combination treatment with lenvatinib and PD-1/L1 mAb showed significant and superior antitumor effects compared with either compound alone. 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 (Kato Y, et al., 2015). Because TAM cells produced interleukin 10 (IL-10) and transforming growth factor, beta 1 (TGFβ) (Noy R, et al., 2014), lenvatinib might increase antitumor immunity in the CT26 model and up-regulate the effect of the PD-1 signal inhibitors.

Thus, immune-modulating effect of lenvatinib may result in potent combination effect with PD-1 signal inhibitors.

7.2.2 Clinical Studies

7.2.2.1 E7080-A001-111 (Phase 1b/2 of Lenvatinib Plus Pembrolizumab for Selected Solid Tumors in US)

E7080-A001-111 (Study 111) is an open-label Phase 1b/2 study in subjects with selected solid tumors (NSCLC, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma [excluding uveal melanoma]), which is conducted in US.

In Phase 1b, subjects were to enroll in 1-3 dose levels to determine and confirm the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib in combination with pembrolizumab. The dose of pembrolizumab did not change during the MTD phase, while lenvatinib started at 24 mg and then be reduced, if necessary, to either 20 mg or 14 mg. In the lenvatinib 24 mg cohort, 2 DLTs were observed in the first 3 subjects (2 renal cell carcinoma and 1 NSCLC): Grade 3 fatigue and Grade 3 arthralgia. The dose was de-escalated to 20 mg/day lenvatinib and 10 additional subjects (total of 6 renal cell carcinoma, 1 NSCLC, 1 Melanoma and 2 Endometrial) started the treatment. There were no DLTs in the lenvatinib 20 mg cohort, and the MTD and RP2D are confirmed at 20 mg lenvatinib once daily (QD) in combination with 200 mg Q3W of pembrolizumab.

In Phase 2, subjects are assigned by tumor type to up to 6 cohorts to receive the MTD to assess the safety and efficacy of the combination in the selected tumor-types. This phase is ongoing.

7.2.2.2 E7080-J081-116 (Phase 1b of Lenvatinib Plus Pembrolizumab for Hepatocellular Carcinoma in Japan and US)

E7080-J081-116 (Study 116) is an open-label, single arm, multicenter, Phase 1b study in subject with hepatocellular carcinoma, which is conducted in Japan and US. Primary objective of this study is to evaluate the tolerability and safety of lenvatinib in combination with pembrolizumab in subjects with Hepatocellular Carcinoma. This study is ongoing.

7.3 Study Rationale

This is a Phase 1b study of lenvatinib in combination with pembrolizumab in Japanese subjects with selected solid tumors (NSCLC, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma [excluding uveal melanoma]). Lenvatinib will be administered at starting dose of 20 mg QD in combination with pembrolizumab 200 mg Q3W. DLT will be evaluated during Cycle 1 (21 days following the initial dosing) to confirm the tolerability and safety. Treatment will continue until disease progression, development of intolerable toxicity, subject requests to discontinue, withdrawal of consent, or study termination by sponsor.

The tolerability and safety for combination of lenvatinib 20 mg QD at starting dose and pembrolizumab 200 mg Q3W, which was determined asMTD and RP2D in Study 111, will be confirmed in Japanese subjects in this Study 115.

Lenvatinib monotherapy was tolerated up to the dose of 24 mg QD continuous administration in Japanese patients with solid tumor, and similar results were observed in Europe and US. Regarding pembrolizumab, which has not been approved in Japan at this time, there has been no significant difference in tolerability and pharmacokinetics noted between Japanese and non-Japanese patients. However, the combination regimen of lenvatinib and pembrolizumab has never been studied in Japan; therefore, the tolerability and pharmacokinetics in Japanese patients are still unknown.

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W, which is the recommended dose of pembrolizumab based on the well-established safety and efficacy profile in solid tumors.

In KEYNOTE-001, an open-label Phase I study was conducted to evaluate the safety, tolerability, PK and pharmacodynamics, and anti-tumor activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose has been identified. In addition, 2 randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been

completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. PK properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

There has been no significant difference in tolerability and PK profile noted between Japanese and non-Japanese patients.

The pembrolizumab 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as above.

Based on above, this study was considered scientifically rational and designed based on the previous findings to evaluate the tolerability, safety, and pharmacokinetics of lenvatinib plus pembrolizumab combination therapy in Japanese subjects.

8 STUDY OBJECTIVES

8.1 Primary Objective

- To confirm the tolerability and safety for combination of lenvatinib plus pembrolizumab in subjects with selected solid tumors

8.2 Secondary Objectives

- To evaluate the following efficacy endpoints by Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) and modified RECIST 1.1:
  - Objective response rate (ORR)
  - Duration of response (DOR)
- To assess the pharmacokinetic (PK) profile of lenvatinib and pembrolizumab
- To detect anti-drug antibodies for pembrolizumab (ADA)

8.3 Exploratory Objectives

- To evaluate the following efficacy endpoints by irRECIST and modified RECIST 1.1:
  - Progression-free survival (PFS)
  - Time to response (TTR)
  - Disease control rate (DCR)
  - Clinical benefit rate (CBR)
- To investigate the relationship between candidate biomarkers and anti-tumor activity of lenvatinib in combination with pembrolizumab:
  - To explore blood and tumor markers (such as programmed cell death protein 1 ligand [PD-L1] expression levels, cytokine and angiogenic factor profiling), and immune cell profiling and evaluate their relationship with clinical outcomes including anti-tumor activity of lenvatinib in combination with pembrolizumab

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E7080-J081-115 is an open-label Phase 1b study. This study will confirm the tolerability and safety of lenvatinib in combination with pembrolizumab in subjects with selected solid tumors. Subjects in this study will have one of the following tumors: non-small cell lung cancer, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma (excluding uveal melanoma).

This study will begin with lenvatinib 20 mg/day orally and pembrolizumab 200 mg (every 3 weeks [Q3W], intravenous [IV]) in subjects with selected solid tumors on a 21-day treatment cycle. For the confirmation of the tolerability of the dose level, dose limiting toxicities (DLTs) will be evaluated during the first cycle (21 days).

If 0 or 1of 6 subjects in a given dose level cohort experiences a DLT, the dose level will be considered tolerable (Figure 1).

Enrollment will be interrupted if 2 or more DLTs are observed at any dose level, and after sponsor and investigators' review, enrollment may continue for up to 6 subjects based on the nature and severity of the DLTs. Once 6 subjects are enrolled, then, 4 additional subjects (10 subjects in total) will be added and that dose level will be considered tolerable if DLT is observed in 3 or less of the10 subjects in total (Figure 1). An independent medical advisor as third party should be consulted for the review as needed.

A lower dose level of lenvatinib of 14 mg QD in combination with 200 mg pembrolizumab Q3W or study discontinuation will be considered, if 20 mg lenvatinib plus 200 mg pembrolizumab dose level is not tolerable, upon discussions between the sponsor and investigators (Figure 1), and the protocol will be amended as necessary. An independent medical advisor as third party should be consulted for the consideration as needed.

If there is a potential subject who is not evaluable for DLT (eg, subject who fails to administer ≥75% of the planned dosage of lenvatinib due to a reason other than treatment related toxicity during Cycle 1), the investigator and sponsor will discuss wheter or not to include the subject in the DLT Analysis Set. If subject is not evaluable for DLT then the subject will be replaced.

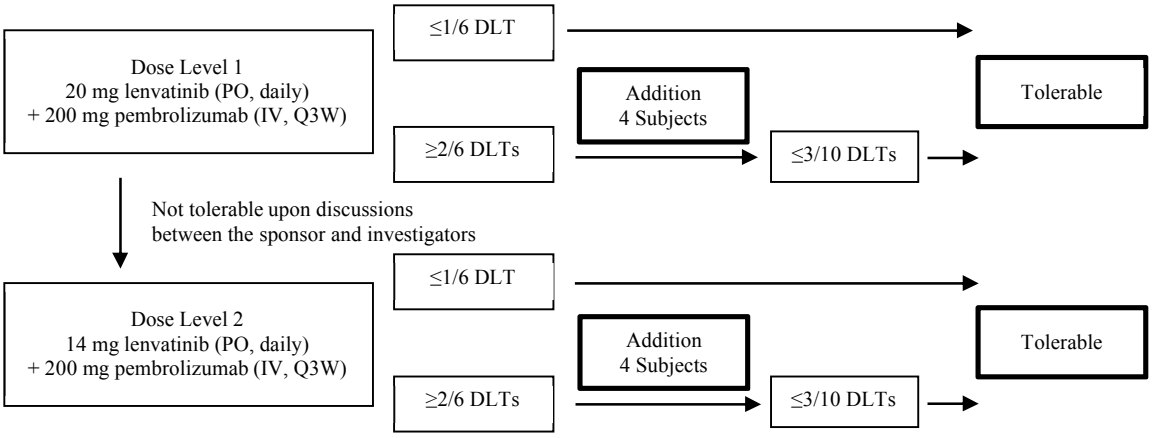


Figure 1 Confirmation of the Tolerability

DLT = dose limiting toxicity, IV = intravenous, PO = per os, Q3W = every 3 weeks.

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 in Cycle 1
- Greater than 2 weeks delay in starting pembrolizumab in 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 1 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 1 hour, with life-threatening consequences and urgent intervention indicated.

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.

The study will be conducted in 3 phases: a Pretreatment Phase, a Treatment Phase, and an Extension Phase (Figure 2).

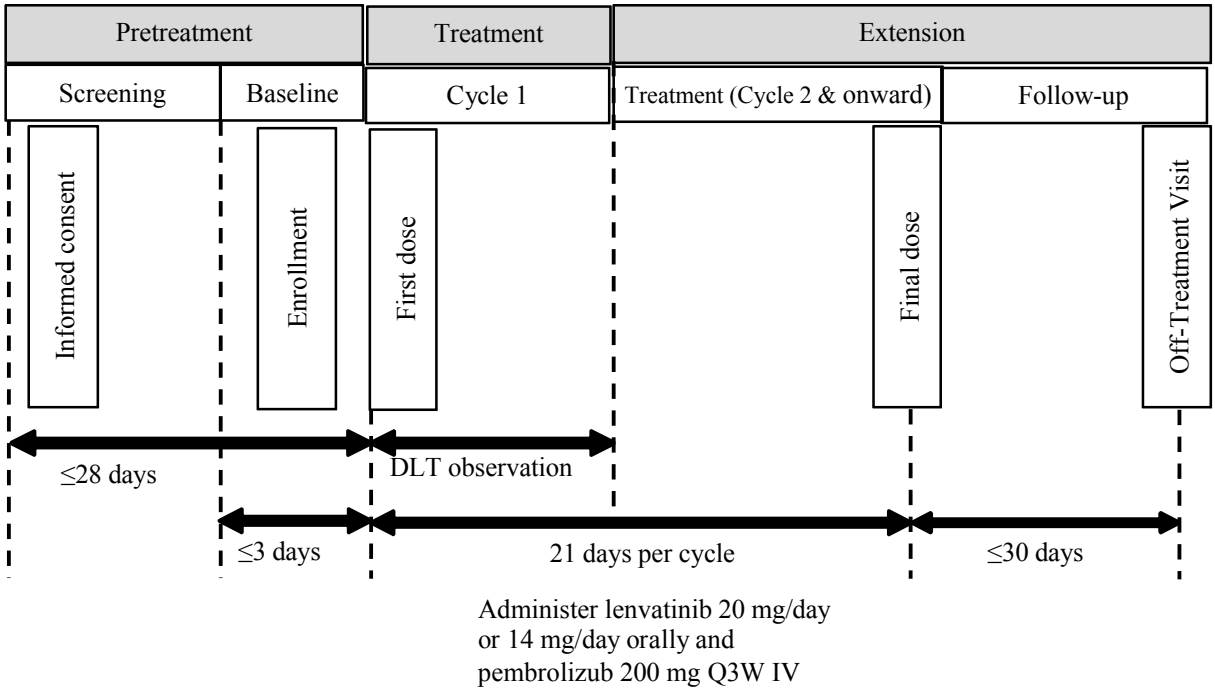


Figure 2 Study Design

DLT = dose limiting toxicity, IV = intravenous, Q3W = every 3 weeks.

9.1.1 Pretreatment Phase

The Pretreatment Phase will last no longer than 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 Cycle 1/Day 1 (C1D1) 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 consists of the first cycle (21 days) for each subject. The Treatment Phase for each subject ends after they complete Cycle 1 of treatment or if 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.

Subjects will be required to stay at the site during Cycle 1 in principle; however, they may be allowed to receive treatment as outpatient at the investigators' discretion based on the safety of the subject.

9.1.3 Extension Phase

The Extension Phase begins after a subject completes Cycle 1 and ends when the subject completes the Off-Tx Visit. Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor termination of the study. 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 who discontinue study treatment transition to the Off-Tx Visit of the Follow-up Period of the Extension Phase.

9.1.3.2 Follow-up Period

The Follow-up Period consists of the Off-Tx Visit. The Off-Tx Visit will occur within 30 days following the last dose of study treatment. Subjects may receive other anti-cancer treatment within 30 days after the final administration if his/her cancer conditions necessitate. In this case, off-treatment observation must be conducted before initiation of other anti-cancer treatment.

9.2 Discussion of Study Design

The study design follows well-established designs for Phase 1b 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 tyrosine kinase inhibitor (TKI) with a PD-1 inhibitor. The tumor types to be studied in this study (non-small cell lung cancer, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of head and neck, or melanoma [excluding uveal 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. This study will enroll between 6 and 10 evaluable subjects with selected solid tumors.

9.3.1 Inclusion Criteria

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

1. Histologically and/or cytologically confirmed selected solid tumor types that have progressed after treatment with standard therapies or for which there are no other appropriate 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. The selected tumor types are: non-small cell lung cancer, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma (excluding uveal melanoma).
2. At least 1 measurable target lesion according to modified RECIST1.1
3. Subjects must have an Eastern Cooperative Oncology Group (ECOG)-Performance Status (PS) of 0 to 1.
4. 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/Day 1 (C1D1)
5. Adequate renal function defined as creatinine ≤1.5 times the upper limit of normal (ULN) or calculated creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula with creatinine levels >1.5×ULN
6. 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
7. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5
8. Adequate liver function as evidenced by bilirubin ≤1.5×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 must be separated from the total and used to assess the liver function instead of the total ALP.

9. Males or females age ≥20 years at the time of informed consent
10. Life expectancy of 12 weeks or more
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.
12. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.
13. Archival tumor tissue or a newly obtained biopsy must be available prior to the first dose of study drug for biomarker analysis. Subjects 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

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

1. Prior anticancer treatment within 28 days (or 5 times the half-life, whichever is shorter) or any investigational agent within 28 days prior to the first dose of study drugs. All toxicities related to prior treatments must be resolved to Grade ≤1 (except alopecia).
   Note: Refer to inclusion criteria regarding Hypertention.
2. 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.
3. Prior treatment with lenvatinib or any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, excluding cancer types such as melanoma and non-small cell lung cancer where prior treatment with one anti-PD-1, anti-PD-L1, or anti-PD-L2 agent is allowed.
4. Subjects must have recovered adequately from any complications from major surgery prior to starting therapy.
5. Subjects having ≥2+ 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.
6. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib
7. 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
8. Prolongation of QTc (Fridericia formula) interval to >480 ms

9. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug
10. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (eg, carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
11. Active infection (any infection requiring systemic treatment)
12. Subject is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C.
13. Serious nonhealing wound, ulcer, or bone fracture
14. Known intolerance to either of the study drugs (or any of the excipients)
15. History of organ allograft
16. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical study
17. 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
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 7.5 mg/d of prednisone or equivalent) may be approved after consultation with the sponsor.
19. 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 [T4], 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, or has a history of interstitial lung disease.
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.
22. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
23. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
24. Females of childbearing potential* who:
    - do not agree to use a highly effective method of contraception for the entire study period and for 120 days after study drug discontinuation ie:
        - total abstinence (if it is their preferred and usual lifestyle)
        - an intrauterine device (IUD) or hormone releasing system (IUS)

- a contraceptive implant
- an oral contraceptive** (with additional barrier method)

OR

- do not have a vasectomized partner with confirmed azoospermia.

For sites outside of the European Union (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 [i.e., 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.

25. 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 Exclusion Criterion #24) 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.

9.3.3 Removal of Subjects From Therapy or Assessment

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

assessments until disease progression is documented or another anticancer therapy is initiated. The investigator will discontinue the study of the subject in the event of the sponsor request to discontinue the study for medical reasons or any other reason (see Section 11.11).

9.3.3.1 Discontinuation Criteria by Subject

If a subject meets any of the following criteria, the investigor will discontinue treating a subject with study treatment or withdraw the subject from the study.

1. Evidence of disease progression or emergence of new lesion(s). (Treatment decisions by the investigator will be based on irRECIST.) If irPD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact sponsor to discuss continuing treatment (see Section 9.5.1.3).
2. Withdrawal of consent by subject
3. Presence of adverse event that prohibits continuation with therapy
4. Pregnancy
5. Subject is turned to be non-compliant with the protocol and ineligible in view of safety issue.
6. Study discontinuation is appropriate judged by the investigator or subinvestigator.
7. Subject is found to be ineligible after the registration.

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. On Day 1 of each cycle, in case concomitantly administered, it will be administered approximately within 1 hour after completion of pembrolizumab administration.

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.

Pembrolizumab will be administered until 2 years after C1D1 at the longest.

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 Day 1 of each cycle (except for Cycle 2) due to administrative reasons. Study treatment with pembrolizumab of Cycle 3 should be skipped if pembrolizumab is administered on Day 4 or later in Cycle 2 due to treatment-related toxicity or any other reason.

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

9.4.1.3.1 CYCLE 1

Dose Modificaton in the Event of DLT

Lenvatinib and infusion of pembrolizumab should be interrupted immediately. Treatment may be resumed in Cycle 2 of pembrolizumab at the same dose (except the toxicity which requires the permanent discontinuation according to the guidance) and at 1 lower dose level of lenvatinib if toxicity is resolved to Grade 0–1 (or torelable Grade 2 in case of lenvatinib treatment-related toxicity) or baseline and investigators decides to continue the study.

Dose Modificaton in the Event of No DLT

Lenvatinib will be interrupted if judged to be clinically needed by investigators, and may be resumed at the same dose level at appropriate timing.

9.4.1.3.2 CYCLE 2 AND ONWARD

Lenvatinib

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the guidelines provided in Table 2 and Table 3, respectively, for this study.

For management of hypertension and proteinuria, refer to the 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 (4 mg every other day) must be discussed with the sponsor. Once the dose has been reduced, it cannot be increased at a later date.

Table 2 Dose Modifications for Lenvatinib

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		

BMI = body mass index.
a: An interruption of lenvatinib treatment for more than 21 days will require a discussion with the sponsor before treatment can be resumed.
b: Excluding alopecia. Initiate optimal medical management for nausea, vomiting, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.
c: Applicable only to Grade 2 toxicities judged by subject and/or physician to be intolerable.
d: Obese subjects with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1 weight loss). These subjects will restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they reached the normal BMI (if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e: 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 should be consulted to obtain permission to continue treatment.

Table 3 Dose Reduction Recommendations for Lenvatinib in Combination With Pembrolizumab

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

QD = once daily.
a. Consult 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 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 1 week 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

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 Table 4 below. See Section 9.4.1.5 for supportive care guidelines, including use of corticosteroids.

Table 4 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when subjects are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.

Table 4 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4 Recurrent 2	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c, d]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, T1DM = type 1 diabetes mellitus.

a: For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

b: If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 5 (Infusion Reaction Treatment Guidelines).

c: Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

d: For asymptomatic Grade ≥3 elevations of amylase and lipase, the sponsor should be consulted to obtain permission to continue treatment.

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.

9.4.1.4 Supportive Care Guidelines for Lenvatinib

9.4.1.4.1 MANAGEMENT OF HYPERTENSION

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP of ≤150/90 mmHg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before 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 mmHg or diastolic BP ≥90 mmHg) 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 mmHg or diastolic BP ≥90 mmHg 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 mmHg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the subject has been on the same hypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

During the Treatment Phase and the Treatment Period in the Extension Phase, subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 or more frequently as clinically indicated until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months. If a repeat event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months.

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

- Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving antihypertensive medication.
- For those subjects already on antihypertensive medication, dose or medication choice should be modified as per the investigator.
- If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 lower dose level 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.

9.4.1.4.2 MANAGEMENT OF PROTEINURIA

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

- Initial episode of proteinuria: If proteinuria ≥2+ is detected on urine dipstick testing, study drug will be continued and a 24-hour urine collection for total protein will be obtained as soon as possible within 72 hours to verify the grade of proteinuria. Grading according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Appendix 3) will be based on the 24-hour urine collection for total protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 2.
- During the Treatment Phase and the Treatment Period in the Extension Phase, urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 of each cycle or more frequently as clinically indicated, until the results have been 1+ or negative for 3 consecutive months. Any subsequent increases in the level of proteinuria higher than 2+ on urine dipstick testing must be confirmed with a 24-hour urine collection and graded according to the dose reduction and interruption instructions provided in the Table 2. If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 3 consecutive months.

9.4.1.4.3 MANAGEMENT OF HEPATOTOXICITY

Regular monitoring of liver function tests (eg, ALT, 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. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, the study drug must be discontinued.

9.4.1.4.4 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, deep vein thrombosis (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. 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.

9.4.1.4.5 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. PRES is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of PRES. 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 the Investigator's Brochure for further information on lenvatinib, including the full set of special warnings and precautions for use.

9.4.1.4.6 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.

9.4.1.4.7 MANAGEMENT OF GASTROINTESTINAL PERFORATION OR FISTULA FORMATION

Study treatment should be discontinued in any subjects who develop gastrointestinal perforation or life-threatening fistula.

9.4.1.4.8 MANAGEMENT OF DIARRHEA

An anti-diarrheal agent should be recommended to the subject at the start of study treatment and subjects should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the subject's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 2 of the protocol should be followed.

9.4.1.5 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 adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous 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.

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

- Pneumonitis:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events or recurrent Grade 2**, immediately treat with intravenous steroids. Administer additional antiinflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- Diarrhea/Colitis:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience 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. For Grade 2 or higher diarrhea, consider gastrointestinal (GI) consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA):
  - For **T1DM** or **Grade 3-4 Hyperglycemia**
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- Hypophysitis:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- Hyperthyroidism or Hypothyroidism:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, nonselective beta-blockers (eg, propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism:
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- Hepatic:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- Renal Failure or Nephritis:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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 deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.**	Subject may be premedicated 1.5h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further study treatment administration.**	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

CTCAE = Common Terminology Criteria for Adverse Events v4.03, 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.

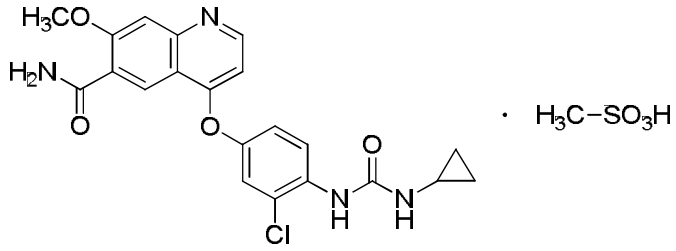
Lenvatinib will be provided as 4-mg and 10-mg capsules. Lenvatinib is formulated with calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, and talc.

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 intravenous 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 intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection.

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 $C_{21}H_{19}ClN_4O_4 \bullet CH_4O_3S$, 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 humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin

with an approximate molecular weight of 149 kDa. (See Appendix for KEYTRUDA® package insert.)

9.4.2.3 Labeling for Study Drug

The following information has to be labeled:

- For clinical study use only
- Name and address of the sponsor
- Chemical name or drug identifier
- Lot number or batch number
- Storage conditions, expiration date if necessary

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 pharmacist or its designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. 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

As for the evaluating of lenvatinib in combination with pembrolizumab, an open-label Phase 1b/2 study in subjects with selected solid tumors (Study 111) is conducting in US. In Phase 1b of Study 111, subjects were to enroll in 1-3 dose levels to determine and confirm the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib in combination with pembrolizumab. The dose of pembrolizumab did not change during the MTD phase, while lenvatinib started at 24 mg and then be reduced, if necessary, to either 20 mg or 14 mg. In the lenvatinib 24 mg cohort, 2 DLTs were observed in the first 3 subjects. The dose was de-escalated to 20 mg/day lenvatinib and 10 additional subjects started the treatment. There were no DLTs in the 2nd cohort, and the MTD and RP2D are confirmed at 20 mg lenvatinib QD in combination with 200 mg Q3W of pembrolizumab. Therefore, the starting dose of lenvatinib and the dose of pembrolizumab in this study are set to 20 mg/day QD and 200 mg Q3W, respectively.

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. On Day 1 of each cycle, in case concomitantly administered, 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 Day 1 of each cycle (except for Cycle 2) due to administrative reasons. Study treatment with pembrolizumab of Cycle 3 should be skipped if pembrolizumab is administered on Day 4 or later in Cycle 2 due to treatment-related toxicity or any other reason.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study drug will be recorded. A concomitant therapy will not be recorded if other anticancer treatment is started.

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

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 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 4 for a summary of clinical findings).

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

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. 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 Pretreatment, Treatment, and Extension 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: Palliative radiotherapy of up to 2 painful pre-existing, non-target bone metastases without being considered progressive disease may be considered on an exceptional 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, 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 clinical interest 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.

The following concomitant medications are **allowed**:

- Thyroid hormone suppressive therapy
- Adjuvant hormonal therapy for history of definitively treated breast or prostate cancer
- Anticoagulants including LMWH, warfarin, anti-Xa agents
- Antiinflammatory agents (Note: use of steroids is not permitted except as outlined in Section 9.4.1.5 to manage immune-related adverse event [irAEs])
- Bisphosphonates
- Supportive care guidelines for pembrolizumab (see Section 9.4.1.5)
- 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

The pharmacist or its designee will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Japan's GCP guidelines as well as other 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 pharmacist or its designee 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, and (d) documentation of returns to 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. Upon completion of drug accountability and reconciliation procedures by the pharmacist's or its designee's personnel and documentation procedures by the sponsor's personnel, all unused study drugs are to be returned to the sponsor. Study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives.

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race and ethnicity. Baseline characteristics will include ECOG-PS, New York Heart Association (NYHA) cardiac disease classification, tumor-node-metastasis (TNM) staging at initial diagnosis, and tumor mutation status (Appendix 2, Appendix 4).

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.

The following prior therapy and diagnosis on the primary disease will also be investigated:

1. First tumor diagnosis (date of diagnosis, diagnostic method [histology/cytology], histological type, staging [TNM classification])

2. Previous anti-cancer therapy for primary disease
   a. Surgical therapy (date, surgical procedure)
   b. Radiotherapy (site of radiotherapy, end date of radiotherapy)

c. Anti-cancer medication (medication name, initial dose, start/end date of medication, reason for discontinuation)
d. Other anti-cancer procedure (procedure name, end date of procedure)

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 10). 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 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. They must be accessible in the event of a sponsor request to submit them for central review.

Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks (±1 week; counting from C1D1) until Week 24, then every 9 weeks (±1 week) during treatment cycles in the Extension Phase. Computed tomography (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 C1D1), at all tumor assessment time points, and as indicated clinically. Color photographs containing a milimeter 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 (scans before informed consent would be acceptable). Subjects with squamous cell carcinoma of head and neck (HNSCC) must also have head and neck scans performed.

The CT scan should be a diagnostic quality spiral or multidetector CT with 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 (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 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 (except for subjects with HNSCC), a follow-up brain scan must be performed to confirm irCR or if clinically indicated.

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

Subjects going off treatment without disease progression (excluding the subject with CR at off-treatment visit) will also undergo tumor assessments per the Schedule of Procedures/Assessments until disease progression is documented or another anticancer therapy is initiated. The investigator will discontinue the study of the subject in the event of the sponsor request to discontinue the study for medical reasons or any other reason (see Section 11.11).

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 (except for subjects with HNSCC) at Screening, every 24 weeks (as needed), or sooner if clinically indicated, and at confirmation of irCR. A bone scan (^{99}m-technetium-based scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases will be performed within 6 weeks prior to 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 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 stable disease (irSD) to be considered the best overall response (BOR), 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. Responses (irPR 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 progressive disease (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 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 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-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]). Responses (PR or CR) should be confirmed no less than 4 weeks after the initial response, but generally at the next scheduled tumor assessment time point. In order for SD to be considered BOR, it must occur ≥5 weeks following the first dose of study drug.

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, TA = tumor assessment.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

A schedule of lenvatinib and pembrolizumab PK, pharmacodynamic, and pharmacogenomic sampling is shown in the Schedule of Procedures/Assessments (Table 10).

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Plasma Lenvatinib and Serum Pembrolizumab Concentrations

Plasma concentrations of lenvatinib and serum concentrations of pembrolizumab will be measured. Blood samples will be collected as specified in Table 10. Table 7 presents the detailed blood sampling schedule for pharmacokinetic assessments. See the Laboratory Manual for a description of collection, handling, and shipping procedures for PK samples.

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

The actual time and date of PK blood collection will be recorded on the CRF. The actual time, date, and dose of lenvatinib administered on Days 1, 14, and 15 of Cycle 1 will be recorded in the CRF. The actual start/stop time of infusion, date, and dose of pembrolizumab administered will be recorded in the CRF. Date and time of last food intake before study drug administration on Days 1 and 15 of Cycle 1 will also be recorded in the CRF.

Table 7 Blood Sampling Schedule for Pharmacokinetic Assessments

Lenvatinib

Days	Time (on each Day)	Acceptable time-window (approximate)
C1D1	Predose of pembrolizumab	≤24 h before infusion
	1 h postdose of lenvatinib	±15 min
	2 h postdose of lenvatinib	±15 min
	4 h postdose of lenvatinib	±15 min
	8 h postdose of lenvatinib	±60 min
	24 h postdose of lenvatinib	≤–60 min
C1D15	Predose of lenvatinib	≤–60 min
	1 h postdose of lenvatinib	±15 min
	2 h postdose of lenvatinib	±15 min
	4 h postdose of lenvatinib	±15 min
	8 h postdose of lenvatinib	±60 min
	24 h postdose of lenvatinib	≤–60 min

Table 7 Blood Sampling Schedule for Pharmacokinetic Assessments

Pembrolizumab

Days	Time (on each Day)	Acceptable time-window (approximate)
C1D1	Predose of pembrolizumab	≤24 h before infusion
C2D1	Predose of pembrolizumab	≤24 h before infusion
C4D1	Predose of pembrolizumab	≤24 h before infusion
C6D1	Predose of pembrolizumab	≤24 h before infusion
C8D1	Predose of pembrolizumab	≤24 h before infusion
Day 1 in every 4 cycles after Cycle 8	Predose of pembrolizumab	≤24 h before infusion
End of treatment	Within 30 days after discontinuation or until the initiation of other anticancer treatment, whichever earlier	–

C#D# = Cycle #/Day #.

Serum Anti-pembrolizumab Antibodies (ADA)

Serum ADA will be measured.

Blood samples will be collected as specified in Table 10. Table 8 presents the detailed blood sampling schedule for anti-pembrolizumab antibodies (ADAs). See the Laboratory Manual for a description of collection, handling, and shipping procedures for blood samples.

Serum ADA will be detected by using validated methods.

The actual time and date of blood collection for ADA will be recorded on the CRF.

Table 8 Blood Sampling Schedule for Anti-pembrolizumab Antibodies (ADAs)

Anti-pembrolizumab Antibodies (ADA)

Days	Time (on each Day)	Acceptable time-window
C1D1	Predose of pembrolizumab	≤24 h before infusion
C2D1	Predose of pembrolizumab	≤24 h before infusion
C4D1	Predose of pembrolizumab	≤24 h before infusion
C6D1	Predose of pembrolizumab	≤24 h before infusion
C8D1	Predose of pembrolizumab	≤24 h before infusion
Day 1 in every 4 cycles after Cycle 8	Predose of pembrolizumab	≤24 h before infusion
End of treatment	Within 30 days afeter discontinuation or until the initiation of other anticancer treatment, whichever earlier	–

C#D# = Cycle #/Day #.

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 10).

Blood samples for the development of exploratory predictive biomarkers will be collected from consented subjects prior to the first dose of study drug, on Cycle 1/Day 15 (C1D15), and on Day 1 of subsequent cycles up to and including Cycle 18, 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 (subjects with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the sponsor). An archival tumor sample from the most recent surgery or biopsy will be collected. 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 serum 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 consented subjects for potential assessment of mutations and other genetic alterations or genes and/or proteins including PD-1/PD-L1/PD-L2 status and other relevant biomarkers (eg, tumor infiltrating lymphocytes, T-cell repertoire, ribonucleic acid [RNA] signature profiles mutational load), 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/PD-L2 status, submission of FFPE tumor 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.

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 and investigators judge that it is medically acceptable to have a biopsy).

A blood plasma sample to isolate circulating cell free nucleic acids (cf-nucleic acids) and a whole blood sample for immune cell profiling will be collected from consented subjects prior to the first dose of study drug (C1D1), and then pre-dose on C1D15 and Day 1 of subsequent cycles up to and including Cycle 18 and at the off-treatment assessment. Cf-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. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor and to assess the immune response.

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. All analyses will be limited to correlations relevant to diseases and clinical ourcomes related to therapy of lenvatinib and pembrolizumab. 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 CTCAE v4.03 grades (for both increasing and decreasing severity), and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and electrocardiogram (ECGs); echocardiograms or multigated acquisition (MUGA) scans including left ventricular ejection fraction (LVEF); and performance of physical examinations as detailed in Table 10.

9.5.1.5.1 Adverse Events and Events Associated with Special Situations

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the 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. For SAEs, all events occurring until 30 days after the subject's last dose will be collected. From 30 days after the last dose, SAEs will be collected through 90 days after the last dose or until 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.

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 adverse event 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 adverse event.

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

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

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

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).

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 "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

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

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 9. The Schedule of Procedures/Assessments (Table 10) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. Clinical laboratory tests will be performed by the local laboratory.

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).

Table 9 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential INR[b]
Clinical Chemistry	
Electrolytes	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[c]	Glucose, ketones, pH, protein, blood (or hemoglobin), specific gravity

RBC = red blood cell, WBC = white blood cell, INR = International Normalized Ratio, T4 = thyroxine, TSH = thyroid stimulating hormone.
a: Thyroid function will be assessed every 2 cycles.
b: Only at Screening/Baseline and when clinically indicated.
c: 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.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to pembrolizumabadministration 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. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF. If AEs were assessed during unscheduled visits, all the data corresponding to the laboratory abnormality will be recorded on the CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 10) by a validated method. BP and pulse will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person. For subjects with an elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), confirmation should be obtained by performing 2 measurements a minimum of

1-hour apart. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart.

Height will be measured at the Screening Visit only.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 10). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 10). 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.

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

9.5.1.5.7 ECHOCARDIOGRAM OR MULTIPLE GATED ACQUISITION SCAN

A MUGA scan (using technetium-99m-pertechnetate) or an echocardiogram to assess LVEF will be performed as designated in the Schedule of Procedures/Assessments (Table 10). 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.

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 10 present the schedule of procedures and assessments for the study.

Table 10 Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

CRF	Phase	Pretreatment		Treatment			Extension		
	Period	**Screening[a]**	**Baseline[a]**	**Cycle 1[b]**			**Treatment (Cycle 2[b] & Beyond)**		**Follow-up Period**
	Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**Off-Treatment Visit[v]**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	Within 30 days after last dose
	Assessments								
S	Informed consent	X							
S	Inclusion/exclusion	X	X						
S	Demographic data	X							
S	ECOG-PS/NYHA[c]	X	X				X		X
S	TNM staging at diagnosis	X							
NS	Medical/surgical history	X							
S	Prior medications	X							
S	Vital signs[d]	X	X	X	X	X	X	X[w]	X
NS	Physical examination[e]	X	X[f]	X	X	X	X		X
NS	12-lead ECG[g]	X		X			X		X
S	MUGA or echocardiogram[x]	X		X					
S	Clinical chemistry & hematology[h, y]	X	X		X	X	X		X
S	Thyroid function tests[h y]	X	X				X[h]		X
S	Urinalysis (Dipstick)[i y]	X	X		X	X	X	X[w]	X
S	Pregnancy test[j y]	X	X						
S	Lenvatinib treatment			Throughout					

Table 10 Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

CRF	Phase	Pretreatment		Treatment			Extension		
	Period	**Screening[a]**	**Baseline[a]**	**Cycle 1[b]**			**Treatment (Cycle 2[b] & Beyond)**		**Follow-up Period**
	Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**Off-Treatment Visit[v]**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	Within 30 days after last dose
	Assessments								
NS	Pembrolizumab treatment[z]			X			X		
NS	Lenvatinib PK blood samples[k]			X		X			
NS	Pembrolizumab PK blood samples[l]			X			X		X
NS	Anti-pembrolizumab antibodies (ADA) blood samples[m]			X			X		X
S	Tumor assessments: CT (MRI)[n]	X		Counting from C1D1, for the first 24 weeks, every 6 weeks (±1 week), or sooner, if clinically indicated, until documentation of confirmed disease progression. After 24 weeks, tumor assessments must be performed every 9 weeks counting from C9D1 (±1 week), or sooner if clinically indicated, until documentation of confirmed disease progression. Responses and PD must be confirmed at least 4 weeks later (usually at the next tumor assessment time point).					X (unless done within previous 4 weeks or subject discontinued for PD and clinically stable)
NS	CT or MRI of the brain[o]	X		For subjects with previously treated eligible brain metastases, brain scan must be performed at Screening and all tumor assessment time points. For all subjects (except for subjects with HNSCC), follow-up brain scans should be performed to confirm irCR, or if clinically indicated.					X (unless done within 4 weeks and as needed)
NS	Bone scan[p]	X		Bone scans will be performed at Screening (except for subjects with HNSCC), every 24 weeks(as needed), or sooner if clinically indicated, and at confirmation of irCR.					

Table 10 Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases

CRF	Phase	Pretreatment		Treatment			Extension		
	Period	**Screening[a]**	**Baseline[a]**	**Cycle 1[b]**			**Treatment (Cycle 2[b] & Beyond)**		**Follow-up Period**
	Visit	**1**	**2**	**3**	**4**	**5**	**6, 8, 10, 12, etc.**	**7, 9, 11, 13, etc.**	**Off-Treatment Visit[v]**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	Within 30 days after last dose
	Assessments								
S	Archival tumor block or slides[q, t]	X[q]							
S	Fresh Tumor Biopsies (additional consent required)[r]	X[r]					X[r]		
S	Blood sample (serum) for biomarkers[s]			X		X	X		X
S	Biomarker (plasma) sample[s]			X		X	X		X
S	Biomarker (whole blood) sample[s]			X		X	X		X
S	Concomitant medications/therapies[u]	Throughout							
S	AEs/SAEs[u]	Throughout							

ADA = anti-drug antibody, AE = adverse event, BP = blood pressure, C#D# = Cycle #/Day #, CRF = case report form, CT = computed tomography, ECG = electrocardiogram, ECOG-PS = Eastern Cooperative Oncology Group-Performance Status, HNSCC = squamous cell carcinoma of head and neck, irCR = immune-related complete response, LVEF = left ventricular ejection fraction, MUGA = multigated acquisition, MRI = magnetic resonance imaging, NYHA = New York Heart Association, PD = progressive disease, PK = pharmacokinetics, RR = respiratory rate, SAE = serious adverse event, TNM = tumor-node-metastasis.

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 hours 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 4 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). Clinical laboratory assessments may be conducted anytime within 72 hours 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.

d: Assessments will include vital signs (resting BP, pulse, 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.

e: A physical examination will be performed at the Screening or Baseline Visit, on C1D1, C1D8, and C1D15, on Day 1 of each subsequent cycle, at the Off-Treatment Visit assessment, and at any time during the study as clinically indicated.

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 minutes prior to the ECG. During the Treatment Period of the Extension Phase, ECGs will be collected on Day 1 of every cycle.

h: Clinical laboratory tests will be performed by the local laboratory. Clinical chemistry and hematology results must be reviewed prior to administration of study drug on C1D1. 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.).

i: Urinalysis will be performed at Screening, Baseline, C1D8, C1D15, and each study visit of every cycle thereafter. Urinalysis will include glucose, blood (or hemoglobin), 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.

j: 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).

k: Study Treatment PK blood samples drawn predose, 1 (±0.25), 2 (±0.25), 4 (±0.25), 8 (±1), and 24 (–1) hours after the administration on C1D1 and C1D15.

l: Pre-dose (trough) PK samples will be collected within 24 hours before infusion in Cycles 1, 2, 4, 6 and 8, and every 4 cycles thereafter; and within 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy).

m: Anti-pembrolizumab antibody (ADA) samples will be collected within 24 hours before infusion in Cycles 1, 2, 4, 6 and 8, and every 4 cycles thereafter; and within 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy).

n: 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 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. 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 progressive disease) 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. During the Follow-up Period, subjects who have discontinued study treatment without progression (excluding the subject with CR at off-treatment visit) should have disease assessments until disease progression is documented or another anticancer therapy is initiated.

o: 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 and the Extension Phase, CT/MRI of the brain will be performed if clinically indicated, and after a subject achieves an irCR for confirmation. 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.

p: A bone scan (^{99}m-technetium-based scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) to assess bone metastases will be performed within 6 weeks prior to C1D1 (historical scans are acceptable) and then every 24 weeks (within that 24th week) from C1D1 for all tumor types except for HNSCC (as needed), 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.

q: An archival tumor tissue sample must be available prior to first dose. An archival tumor sample from the most recent surgery or biopsy will be collected. If archival tumor tissue sample is not available, please see footnote t.

r: Optional fresh paired tumor biopsies will be collected at the Screening Period 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 and investigators judge that it is medically acceptable to have a biopsy) from consented subjects to examine markers including markers of target engagement, relevant pharmacodynamic biomarkers, and potential markers of response.

s: Collection of blood sample from consented subjects to be used for biomarker studies. Samples will be obtained predose at these timepoints: C1D1, C1D15, Day 1 of all subsequent cycles up to and including Cycle 18, and at the off-treatment assessment.

t: If an archival tumor sample for biomarker analysis is not available from subjects, 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. Subjects with inaccessible tumors for biopsy specimens can be enrolled without a biopsy upon consultation and agreement by the sponsor.

u: Concomitant medications/therapies are recorded for 30 days after last dose or until the subject initiates new anticancer therapy, whichever is earlier. Collection of AE/SAE will be referred to the statement in Safety Assessments.

v: The off-treatment assessment should occur within 30 days after the final dose of study treatment. Subjects may receive other anti-cancer treatment within 30 days after the final administration if his/her cancer conditions necessitate. In this case, off-treatment observation must be conducted before initiation of other anti-cancer treatment.

w: Vital signs and Urinalysis of C2D15 will be conducted. Assessments/procedures on Day 15 of Cycle 3 or later can be skipped only if subject's safety is assured by the investigators.
Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored on Day 15 or more frequently as clinically indicated until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 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.
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+ or negative.
Subjects will visit on the Day 15 if BP monitoring or urine dipstick testing is required as specified above.

x: During the Treatment and Extension Phases, MUGA scans or echocardiograms will be performed to assess LVEF every 24 weeks.

y: 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.

z: Pembrolizumab will be administered until 2 years after C1D1 at the longest. Study treatment with pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle (except for Cycle 2) due to administrative reasons. Study treatment with pembrolizumab of Cycle 3 should be skipped if pembrolizumab is administered on Day 4 or later in Cycle 2 due to treatment-related toxicity or any other reason.

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 10 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, vital signs, ECGs, echocardiograms or MUGA scans, physical examinations and assessment of AEs, are standard evaluations to ensure subject safety.

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

9.5.4.1 Reporting of Serious Adverse Events

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

All serious adverse events occurring until 30 days after the subject's last dose, regardless of causality assessment, must be collected. From 30 days after the last dose, SAEs will be collected through 90 days after the subject's last dose, or until 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 Attachment 1.

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 Attachment 1.

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

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception and exposure to study drug through breastfeeding must be reported until 30 days after the subject's last dose. From 30 days after the last dose, 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 until the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, from 30 days after the last dose, any exposure to study drug through breastfeeding during study treatment or within 120 days of the last study treatment, or until 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 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Attachment 1. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

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

9.5.4.3 Reporting of Events Associated with Special Situations

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

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

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

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

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

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

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor to regulatory authorities in compliance with regulatory requirements and established guidance. The format of these reports will be dictated by the regulatory requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 10).

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.

Subjects who discontinue study treatment prior to completing the Treatment Phase for any reason other than a DLT will 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, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

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

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator 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 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 study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary objective is to confirm the tolerability and safety for combination of lenvatinib plus pembrolizumab in subjects with selected solid tumors. Thus, the primary endpoints will be safety related endpoints including DLT.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints related to the efficacy endpoints will be ORR, $ORR_{(Week\ 24)}$, and DOR by irRECIST and modified RECIST 1.1. These efficacy endpoints are defined as follows.

- **ORR** is defined as the proportion of subjects who have BOR of (ir)CR or (ir)PR at the time of data cutoff.
- **$ORR_{(Week\ 24)}$** is defined as the proportion of subjects who have BOR of $(ir)CR_{(Week\ 24)}$ or $(ir)PR_{(Week\ 24)}$ as of the Week 24 tumor assessment time point.
- **DOR** is defined as the time from the first documentation of (ir)CR or (ir)PR to the date of first documentation of disease progression (based on irRECIST and modified RECIST 1.1) or death (whichever occurs first).

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

Serum ADA will be also measured.

9.7.1.1.3 EXPLORATORY ENDPOINT

The exploratory endpoints related to the efficacy endpoints will be PFS, TTR, DCR, and CBR by irRECIST and modified RECIST 1.1. These efficacy endpoints are defined as follows.

- **PFS** is defined as the time from the first study dose date to the date of first documentation of disease progression (based on irRECIST and modified RECIST 1.1) 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.

- **TTR** is defined as the time from the date of first study dose to the date of first documentation of (ir)CR or (ir)PR.
- **DCR** is defined as the proportion of subjects who have BOR of (ir)CR or (ir)PR or (ir)SD (minimum duration from C1D1 to (ir)SD ≥5 weeks).
- **CBR** is defined as the proportion of subjects who have BOR of (ir)CR or (ir)PR or durable (ir)SD (duration of (ir)SD ≥23 weeks).

The exploratory objective is to investigate the relationship between candidate biomarkers and anti-tumor activity of lenvatinib in combination with pembrolizumab. Exploratory endpoints will be blood and tumor markers (such as PD-L1 expression levels, cytokine and angiogenic factor profiling), and immune cell profiling.

9.7.1.2 Definitions of Analysis Sets

DLT Analysis Set will include all subjects who have completed Cycle 1 without major protocol deviation with at least 75% of study drug compliance and are assessed for DLT, and subjects who have experienced DLT during Cycle 1. This will be the analysis set to confirm tolerability.

Safety Analysis Set/Efficacy Analysis Set will include all subjects who received at least 1 dose of study drug.

PK Analysis Set will include all subjects who have received at least 1 dose of lenvatinib and pembrolizumab, and have evaluable concentration data.

9.7.1.3 Subject Disposition

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

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Efficacy Analysis Set will be summarized for each dose level cohort and overall using descriptive statistics. Continuous demographic and baseline variables include age; categorical variables include sex, age group, race, region, ECOG-PS, NYHA cardiac disease classification, and TNM 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 (WHO DD) 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

Efficacy analyses will be based on the Efficacy Analysis Set. Efficacy data will be presented for each dose level cohort and/or overall as appropriate. BOR will be summarized, and ORR, $ORR_{(Week\ 24)}$, and their corresponding exact 2-sided 95% confidence interval (CI) will be calculated. DOR will also be summarized and plotted over time by Kaplan-Meier method. Likewise, PFS and TTR will be analyzed as needed. If applicable, DCR, CBR, and their corresponding exact 2-sided 95% CI will also be calculated. If applicable, a waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at postbaseline nadir (ie, maximum tumor).

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The primary PK parameters of lenvatinib under combination will be calculated using noncompartmental analysis and compared with historical data after single dose using the PK analysis set. If warranted, additional analyses may be performed. PK data for lenvatinib and pembrolizumab is planned to be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this study and from other studies, a population PK analysis may be performed to characterize PK parameters to support the proposed dosing regimen. PK data for lenvatinib and pembrolizumab may also be used to explore the exposure-response relationships for antitumor activity/efficacy as well as biomarkers and safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately. For serum ADA levels, a listing of results will be made.

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. PK/pharmacodynamic relationships will be explored graphically and may be investigated by model-based analyses. Details of the analyses may be described in a separate analysis plan. The results of these analyses, if performed, will be reported separately.

9.7.1.8 Tolerability/Safety Analyses

All tolerability analyses will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated.

Safety analyses will be performed on the Safety Analysis Set. Safety data will be presented for each dose level cohort and/or overall as appropriate.

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 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 (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during the time from the first dose of study drug to 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or

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

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

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

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. 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.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. 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. 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. 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 (SI) 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 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 overall study period.

9.7.1.8.4 VITAL SIGNS

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

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 using shift tables. Descriptive statistics for ECG parameters and changes from baseline will be presented.

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.

9.7.2 Determination of Sample Size

A sample size of 6 to 10 subjects in this study. This is not based on statistical power considerations.

9.7.3 Interim Analysis

9.7.4 No interim analysis is planned for this study. Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

10 REFERENCE LIST

Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366:2455–65.

Chen L. Co-inhibitory molecules of the B7-CD28 family in the control of T-cell immunity. Nature Rev Immunol. 2004;4:336–347.

Coico R, Sunshine G, Benjamini E. Immunology: A Short Course. 5th ed. Hoboken (NJ): Wiley-Liss; 2003. p. 131.

Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008;8:579-91.Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9:669-76.

Gabrilovich DI, Chen HL, Girgis KR, Cunningham HT, Meny GM, Nadaf S, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med. 1996;2:1096–1103.

Gadiot J, Hooijkaas A, Kaiser A, van Tinteren H, van Boven H Blank C. Overall survival and PD-L1 expression in metastasized malignant melanoma. Cancer. 2011;117:2192–201.

Gao Q, Wang X, Qiu S, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res. 2009;15:971–9.

Gild ML, Bullock M, Robinson BG, Clifton-Bligh R. Multikinase inhibitors: A new option for the treatment of thyroid cancer. Nat Rev Endocrinol. 2011;7:617–624.

Hamid O, Carvajal RD. Anti-programmed death-1 and anti-programmed death-ligand 1 antibodies in cancer therapy. Expert Opin Biol Ther. 2013;13:847-61.

Hattori K, Heissig B, Wu Y, Dias S, Tejada R, Ferris B, et al., Placental growth factor reconstitutes hematopoiesis by recruiting VEGFR1+ stem cells from bone-marrow microenvironment. Nat Med. 2002;8:841-9.

Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279:577-80.

Hirota S, Ohashi A, Nishida T, Isozaki K, Kinoshita K, Shinomura Y, et al. Gain-of-function mutations of platelet-derived growth factor receptor α gene in gastrointestinal stromal tumors. Gastroenterology. 2003;125:660-7.

Huang Y, Chen X, Dikov MM, Novitskiy SV, Mosse CA, Yang L, et al. Distinct roles of VEGFR-1 and VEGFR-2 in the aberrant hematopoiesis associated with elevated levels of VEGF. Blood. 2007;110:624–631.

Kato Y, Matsui J. Effects of Lenvatinib on Tumor-Associated Macrophages Enhance Antitumor Activity of PD-1 Signal Inhibitors. JCA. 2015.

Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, et al. International patterns and trends in thyroid cancer incidence. 1973-2002. Cancer Causes Control. 2009;20:525-31.

Kondo T, Ezzat S, Asa SL. Pathogenetic mechanisms in thyroid follicular-cell neoplasia. Nat Rev Cancer. 2006;6:292-306.

Laakkonen P, Waltari M, Holopainen T, Takahashi T, Pytowski B, Steiner P, et al. Vascular endothelial growth factor receptor 3 is involved in tumor angiogenesis and growth. Cancer Res. 2007;67:593-9.

Matsui J, Wakabayashi T, Asada M, Yoshimatsu K, Okada M. Stem cell factor/c-kit signaling promotes the survival, migration, and capillary tube formation of human umbilical vein endothelial cells. J Biol Chem. 2004;279:18600-7.

Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity. 2014;41:49-61.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Oseini AM, Roberts LR. PDGFRα: a new therapeutic target in the treatment of hepatocellular carcinoma? Expert Opin Ther Targets. 2009;13:443-54.

Phay JE, Shah MH. Targeting RET receptor tyrosine kinase activation in cancer. Clin Cancer Res. 2010;16:5936-41.

Philips GK, Atkins M. Therapeutic uses of anti-PD-1 antibodies. Int Immunol. 2015;27:39-46.

Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014; 384:1109-17.

Sharpe AH, Freeman GJ. The B7–CD28 superfamily. Nature Rev Immunol. 2002;2:116–26.

Shumaker R, Aluri J, Fan J, Martinez G, Thompson, GA, Ren M. Effect of rifampin on the pharmacokinetics of lenvatinib in healthy adults. Clin Drug Investig. 2014;34:651-9.

Shumaker R, Aluri J, Fan J, Martinez G, Thompson GA, Ren M. Effects of ketoconazole on the pharmacokinetics of lenvatinib (E7080) in healthy participants. Clin Pharmacol Drug Dev. 2015;4:155–60.

Stagg J, Allard B. Immunotherapeutic approaches in triple-negative breast cancer: latest research and clinical prospects. Ther Adv Med Oncol. 2013;5(3):169-81.

St Bernard R, Zheng L, Liu W, Winer D, Asa SL, Ezzat S. Fibroblast growth factor receptors as molecular targets in thyroid carcinoma. Endocrinology. 2005;146:1145-53.

Tammela T, Alitalo K. Lymphangiogenesis: Molecular mechanisms and future promise. Cell. 2010;140:460-76.

Terme M, Pernot S, Marcheteau E, Sandoval F, Benhamouda N, Colussi O. VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. Cancer Res. 2013;73:539–549.

Topalian SL, Hodi F, Brahmer J, Gettinger S, Smith D, McDermott D, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med. 2012;366:2443–54.

Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nat Rev Cancer. 2010;10:116-29.

Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet AL, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med. 2015;212:139–148.

Williams D. Cancer after nuclear fallout: lessons from the Chernobyl accident. Nat Rev Cancer. 2002;2:543-9.

CTCAE Reference

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

RECIST Reference

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

KEYTRUDA Package Insert
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

LENVIMA Package Insert
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206947s000lbl.pdf

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 additional approval by the applicable IRB. 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 and the IRB 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 the IRB. In these cases, the sponsor may be required to send a letter to 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.

11.3 Monitoring Procedures

The sponsor'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 head of the medical institution will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with Japan's 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 Japan's GCP. All records at the site are subject to inspection by the local auditing agency and to IRB review.

In accordance with Japan's GCP, 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
- 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 consented 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 items that are not included in any medical records (eg, hospital records, worksheets), the data recorded directly on the CRF are to be considered source data:

- Demographic data (race, ethnicity)
- NYHA cardiac function classification: date of evaluation, NYHA class
- Prior therapy: name, starting and ending date of the medication, starting dose, and reason for discontinuation
- ECG results: normal/abnormal
- Results of follow-up evaluation in subject who discontinued – in all categories
- Tumor diagnosis: TNM classification
- Tumor assessment: presence or absence of target and non-target lesion
- Target lesion: location, size in diameter, evaluation date and time
- Non-target lesion: location, result of evaluation, evaluation date and time
- New lesion: presence or absence, location, and date of confirmation, if present
- Dose and dosing date of lenvatinib and pembrolizumab

- Drug concentration measurement: dates and time of dosing, blood sampling, and food consumptions
- Discontinuation: reason for discontinuation
- Information concerning AEs: CTCAE Grade (for items not specified in CTCAE), outcome, causal relationship to lenvatinib and/or pembrolizumab, severity of the AE, relation to overdose
- Concomitant drug: reason for administration
- Concomitant therapy: type of therapy, reason for use
- Other relevant information

For the items excluding the following items (1 to 6), hospital records will be the source data in principle; however, other appropriate records, if any, may be used as source data.

1. Source data for informed consent
   Informed consent form
2. Source data for tests and examinations
   Test results sheet (and/or electronic data)
3. Source data for pathological assessment
   Test results sheet, medical records provided by other hospital (and/or electronic data)
4. Source data for tumor assessment
   Imaging record (and/or electronic form). CRF is to be considered source data for assessment if it includes measured values
5. Source data for ECG recordings
   Recorded ECG charts (and/or electronic data)
6. Shipping record of samples to outside laboratories
   Shipping slip

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator, 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, ICFs and IRB correspondence). The site should plan to retain study documents until the approval of a marketing application, until at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product as directed by the sponsor, or until at least 3 years have elapsed since the discontinuation or completion of this clinical study, whichever comes later.

Pembrolizumab is expected to be designated as a biologic product. The site will retain and control the sources to identify the name and address of subject, the dosing date, and lot number of study drug for 10 years from the date of last dose (or shipment) for the purpose of traceability.

It is requested that at the completion of the required retention period the site 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 Japan's GCP and all applicable local regulations. A government regulatory authority may request an inspection during the study or after its completion.

11.8 Handling of Study Drug

All study drugs will be supplied to the pharmacist or its designee 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 pharmacist or its designee must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger. 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 pharmacist or its designee 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 pharmacist or its designee will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form (upon request) to the sponsor.

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 and the head of the medical institution. 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 head of the medical institution and the sponsor, 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 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 the Clinical Trial Agreement executed between the sponsor and the head of the medical institution.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Clinical Trial Agreement executed between the head of the medical institution and the sponsor.

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 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 and provide the sponsor and the IRB 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 immune-related response criteria (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 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 longest diameter 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
$SOD_{baseline}$	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 short axis 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 ($SOD_{timepoint}$). Special consideration for target lesions: • If target lesion is too small to measure, a default value of 5 mm should be entered on eCRF. • If target lesion is 5-10 mm, 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 "0 mm" 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 short axis. • 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 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
irNE	Used in exceptional cases where insufficient data exists due to poor quality of scans or missed scans or procedure

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, irPR = immune-related partial response, irSD = immune-related stable disease, NE = Not evaluable.

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

b: Assuming response (irCR or irPR) 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 Common Terminology Criteria for Adverse Events (CTCAE v4.03, published 14 June 2010) provides descriptive terminology to be used for adverse event reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE v4.03 have been correlated with single-concept Medical Dictionary for Regulatory Activities (MedDRA) terms.

The Common Terminology Criteria for Adverse Events v4.03 grading refers to the severity of the AE. The Common Terminology Criteria for Adverse Events grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

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

ADL = activities of daily living, CTCAE = Common Terminology Criteria for Adverse Events.

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

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

Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.03

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

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

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

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

NYHA = New York Heart Association.

Adapted from The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. New York: Little Brown; 1994. p.253-6.

Appendix 5 Clinical Studies Evaluating Drug–Drug Interactions with Lenvatinib

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

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

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

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

Appendix 6 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

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

Collection of the pharmacodynamic, pharmacogenomic, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for pharmacodynamic, pharmacogenomic 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, pharmacogenomic, 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, pharmacogenomic, 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 is available in the FDA website at:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7080-J081-115

Study Protocol Title: An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subjects with Selected Solid Tumors

Investigational Product Name: Lenvatinib (E7080/LENVIMA™) and Pembrolizumab (MK-3475/KEYTRUDA®)

SIGNATURES

Authors:

PPD
PPD
OBG, Eisai Co., Ltd. Date

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Protocol Amendment

Study Drug:	Lenvatinib (E7080)
Study Protocol Number:	E7080-J081-115
Study title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subject with Selected Solid Tumors
Protocol Amendment Number and Date:	Amendment 01: 16 Jun 2017

Original Text	Amended Text
Title Page: **Approval Date** V1.0 14 Sep 2016 (Original Protocol)	V1.0 14 Sep 2016 (Original Protocol) **16 Jun 2017 (Amendment 01)**
Reason of Amendment(s): • Protocol revision	

Original Text	Amended Text
Clinical Protocol synopsis: **Investigators** **To be determined**	~~**Investigators**~~ ~~**To be determined**~~
Reason of Amendment(s): • No need to be included based on the protocol template.	

Original Text	Amended Text
Clinical Protocol synopsis/ 9.3.2: **Exclusion Criteria:** **(Not included)**	**32. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.**
Reason of Amendment(s): • Updated based on the latest pembrolizumab protocol standard text provided by Merck.	

Original Text	Amended Text
Clinical Protocol Synopsis: Dose Interval Modification Guidelines for Non-Hepatic Drug-Related Adverse Events (Table) / 9.4.1.3.2 Table 4: Pneumonitis 3-4 : Permanently discontinue	Pneumonitis 3-4 **or Recurrent 2** : Permanently discontinue
Reason of Amendment(s): • Updated based on the latest pembrolizumab protocol standard text provided by Merck.	

Original Text	Amended Text
7 INTRODUCTION The goal of Study E7080-J081-115, which will be conducted in patients, is to confirm the tolerability and safety for combination of lenvatinib plus pembrolizumab in Japanese subjects with selected solid tumors.	The goal of Study E7080-J081-115, which will be conducted in patients, is to confirm the tolerability and safety for combination of lenvatinib plus pembrolizumab in Japanese subjects with selected solid tumors**: non-small cell lung cancer, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma (excluding uveal melanoma)**.
Reason of Amendment(s): • Description Adjustment.	

Original Text	Amended Text
7.1.2 PD-1 Inhibitors and Pembrolizumab:	
Pembrolizumab [Keytruda (US)], a humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co for the treatment of patients with cancer. Pembrolizumab is approved for treatment of patients with melanoma in several countries; in the US and European Union (EU) it is approved for the treatment of patients with advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of patients with NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should also have disease progression on FDA approved therapy for these aberrations prior to receiving pembrolizumab. **Pembrolizumab has demonstrated initial clinical efficacy in single arm monotherapy trials in subjects with NSCLC, head and neck squamous cell carcinoma, urothelial cancer, 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.**	**Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (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 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 brochure.**

Reason of Amendment(s):

- Updated based on the latest pembrolizumab protocol standard text provided by Merck.

Original Text	Amended Text
7.2.2 Clinical Study (E7080-A001-111) … **(Not included)**	**7.2.2 Clinical Studies** **7.2.2.1 E7080-A001-111 (Phase 1b/2 of Lenvatinib Plus Pembrolizumab for Selected Solid Tumors in US)** … **7.2.2.2 E7080-J081-116 (Phase 1b of Lenvatinib Plus Pembrolizumab for Hepatocellular Carcinoma in Japan and US)** **E7080-J081-116 (Study 116) is an open-label, single arm, multicenter, Phase 1b study in subject with hepatocellular carcinoma, which is conducted in Japan and US. Primary objective of this study is to evaluate the tolerability and safety of lenvatinib in combination with pembrolizumab in subjects with Hepatocellular Carcinoma. This study is ongoing.**
Reason of Amendment(s): - Updated that the study is ongoing.	

Original Text	Amended Text
7.3 Study Rationale **…** **(Not included)**	The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W, which is the recommended dose of pembrolizumab based on the well-established safety and efficacy profile in solid tumors. In KEYNOTE-001, an open-label Phase I study was conducted to evaluate the safety, tolerability, PK and pharmacodynamics, and anti-tumor activity of single agent pembrolizumab.

The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose has been identified. In addition, 2 randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited

	volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. PK properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing. **In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.** **There has been no significant difference in tolerability and PK profile noted between Japanese and non-Japanese patients.** **The pembrolizumab 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as above.**

Reason of Amendment(s):

- Updated based on the latest pembrolizumab protocol standard text provided by Merck.

Original Text	Amended Text
9.3.3 Removal of Subjects From Therapy or Assessment: …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.	…The Discontinuation From Treatment CRF page will be completed indicating the primary reason for discontinuation from treatment. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing CRF page.
Reason of Amendment(s): • Updated based on the latest protocol standard text of Eisai.	

Original Text	Amended Text
9.4.1.5 Supportive Care Guidelines for Pembrolizumab **Pneumonitis:** For Grade 3-4 events, immediately treat with intravenous steroids.	For Grade 3-4 events **or recurrent Grade 2**, immediately treat with intravenous steroids.
Reason of Amendment(s): • Updated based on the latest pembrolizumab protocol standard text provided by Merck.	

Original Text	Amended Text
9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS: 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.**	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.
Reason of Amendment(s): • Updated based on the latest protocol standard text of Eisai.	

Original Text	Amended Text
9.5.2.1 Schedule of Procedures/ Assessments: **Table 9 Schedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases**	
Medical/surgical history Baseline[a] **X**	Medical/surgical history Baseline[a]
Tumor assessments: CT (MRI)[n] Off-Treatment Visit[v] X (unless done within previous 4 weeks or subject discontinued for PD)	Tumor assessments: CT (MRI)[n] Off-Treatment Visit[v] X (unless done within previous 4 weeks or subject discontinued for PD **and clinically stable**)
CT or MRI of the brain[o] Off-Treatment Visit[v] X (unless done within 4 weeks)	CT or MRI of the brain[o] Off-Treatment Visit[v] X (unless done within 4 weeks **and as needed**)
Reason of Amendment(s): • Description Adjustment.	

Original Text	Amended Text
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.	**Any pregnancy in which the estimated date of conception and exposure to study drug through breastfeeding must be reported until 30 days after the subject's last dose. From 30 days after the last dose,** 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 until the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, **from 30 days after the last dose,** any exposure to study drug through breastfeeding during study treatment or within 120 days of the last study treatment, or until the subject initiates a new anticancer therapy, whichever is

	earlier, must be reported

Reason of Amendment(s):

- Changed to revise operational discrepancy.

Original Text	Amended Text
9.5.5 Completion/Discontinuation of Subjects: Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons. **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.**	Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons.

Reason of Amendment(s):

- Updated based on the latest protocol standard text of Eisai.

Protocol Amendment

Study Drug:	Lenvatinib (E7080)
Study Protocol Number:	E7080-J081-115
Study title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subject with Selected Solid Tumors
Protocol Amendment Number and Date:	Amendment 02: 10 Apr 2018

Original Text	Amended Text
Title Page: **Approval Date** V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendment 01)	V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendment 01) **10 Apr 2018 (Amendment 02)**
Reason of Amendment(s): • Protocol revision	

Original Text	Amended Text
Clinical Protocol synopsis: **Study Period and Phase of Development** **Approximately 18 months**	**30 months (plan)**
Reason of Amendment(s): • Updated for extending study period.	

Protocol Amendment

Study Drug:	Lenvatinib (E7080)
Study Protocol Number:	E7080-J081-115
Study title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subject with Selected Solid Tumors
Protocol Amendment Number and Date:	Amendment 03: 05 Apr 2019

Original Text	Amended Text
Title Page: **Approval Date** V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendment 01) 10 Apr 2018 (Amendment 02)	V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendment 01) 10 Apr 2018 (Amendment 02) **05 Apr 2019 (Amendment 03)**
Reason of Amendment(s): • Protocol revision	

Original Text	Amended Text
Clinical Protocol synopsis: **Study Period and Phase of Development** **30 months (plan)**	**42 months (plan)**
Reason of Amendment(s): • Updated for extending study period.	

Protocol Amendment

Study Drug:	Lenvatinib (E7080)
Study Protocol Number:	E7080-J081-115
Study title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subject with Selected Solid Tumors
Protocol Amendment Number and Date:	Amendment 04: 14 Feb 2020

Original Text	Amended Text
Title Page: **Approval Date** V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendment 01) 10 Apr 2018 (Amendment 02) 05 Apr 2019 (Amendment 03)	V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendment 01) 10 Apr 2018 (Amendment 02) 05 Apr 2019 (Amendment 03) **14 Feb 2020 (Amendment 04)**
Reason of Amendment(s): • Protocol revision	

Original Text	Amended Text
Clinical Protocol synopsis: **Assessments** **Efficacy** Subjects going off treatment 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.	Subjects going off treatment without disease progression **(excluding the subject with CR at off-treatment visit)** will also undergo tumor assessments per the Schedule of Procedures/Assessments until disease progression is documented or another anticancer therapy is initiated.
Reason of Amendment(s): • Changed to revise operational discrepancy.	

Original Text	Amended Text
9.3.3 **Removal of Subjects From Therapy or Assessment** 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.	During the Follow-up Period, subjects who have discontinued study treatment without progression **(excluding the subject with CR at off-treatment visit)** should have disease assessments until disease progression is documented or another anticancer therapy is initiated.
Reason of Amendment(s): • Changed to revise operational discrepancy.	

Original Text	Amended Text
9.5.1.3 **Efficacy Assessments** Subjects going off treatment 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.	Subjects going off treatment without disease progression **(excluding the subject with CR at off-treatment visit)** will also undergo tumor assessments per the Schedule of Procedures/Assessments until disease progression is documented or another anticancer therapy is initiated.
Reason of Amendment(s): • Changed to revise operational discrepancy.	

Original Text	Amended Text
Table 10 **AssessmentsSchedule of Procedures/Assessments in the Pretreatment, Treatment, and Extension Phases** n: 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	n: During the Follow-up Period, subjects who have discontinued study treatment without progression **(excluding the subject with CR at off-treatment visit)** should have disease assessments until disease progression is documented or another anticancer therapy is initiated
Reason of Amendment(s): • Changed to revise operational discrepancy.	

Protocol Amendment

Study Drug:	Lenvatinib (E7080)
Study Protocol Number:	E7080-J081-115
Study title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subject with Selected Solid Tumors
Protocol Amendment Number and Date:	Amendment 05: 7 Apr 2020

Original Text	Amended Text
Title Page: **Approval Date** V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendment 01) 10 Apr 2018 (Amendment 02) 05 Apr 2019 (Amendment 03) 14 Feb 2020 (Amendment 04)	V1.0 14 Sep 2016 (Original Protocol) 16 Jun 2017 (Amendment 01) 10 Apr 2018 (Amendment 02) 05 Apr 2019 (Amendment 03) 14 Feb 2020 (Amendment 04) **7 Apr 2020 (Amendment 05)**
Reason of Amendment(s): • Protocol revision	

Original Text	Amended Text
Clinical Protocol synopsis: **Study Period and Phase of Development** **42 months (plan)**	**54 months (plan)**
Reason of Amendment(s): • Updated for extending study period.	