1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-J081-116
Study Protocol Title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subjects with Hepatocellular Carcinoma
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-ku, Tokyo 112 8088 Japan Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	Lenvatinib (E7080/LENVIMA™/ KISPLYX®) and Pembrolizumab (MK-3475/KEYTRUDA®)
Indication:	Hepatocellular carcinoma
Phase:	Phase 1b
Approval Date:	V1.0 21 Sep 2016 (Original Protocol) V2.0 10 Mar 2017 (Amendment 01) V3.0 13 Jul 2017 (Amendment 02) V4.0 12 Feb 2018 (Amendment 03) V5.0 13 Aug 2018 (Amendment 04) V6.0 17 Jan 2019 (Amendment 05)
IND Number:	115650
EudraCT Number:	2018-000522-55
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

Summary of Changes
Revisions to Amendment 01
Date: 10 Mar 2017

Change	Rationale	Affected Protocol Sections
Delete "Investigators: To be determined "	No need to be included based on the protocol template.	• Clinical Protocol synopsis
Exclusion Criterion #17 Change to "Therapy for HCV must be completed at least 4 weeks prior to first dose of study drug in case of Hepatitis C subjects who are on active HCV treatment."	Changed in order to avoid possible confounding toxicity by the therapy for HCV, which was based on the discussion with Merck.	• Clinical Protocol synopsis • Section 9.3.2
New Exclusion Criterion was added (as #18) "Has dual active HBV infection (HBsAg (+) and /or detectable HBV DNA) and HCV infection (anti-HCV Ab(+) and detectable HCV RNA) at study entry."	Added to exclude patients who have dual active HBV and HCV infection, which was based on the discussion with Merck.	• Clinical Protocol synopsis • Section 9.3.2
New Exclusion Criterion was added (as #32) "Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients."	Updated based on the latest pembrolizumab protocol standard text provided by Merck.	• Clinical Protocol synopsis • Section 9.3.2
Study Treatment Dose Modification 2. Cycle 2 and onward (and applies to Cycle 1 **and onward** of Expansion part)	Underlined words were added to make the language clear.	• Clinical Protocol synopsis • Section 9.4.1.3.2
Add requirement that pembrolizumab treatment is to be discontinued for subjects with **recurrent Grade 2 pneumonitis.**	Updated based on the latest pembrolizumab protocol standard text provided by Merck.	• Clinical Protocol synopsis • Section 9.4.1.3.2 (Table 4)
Guidance for Management of Hepatic Events of Clinical Interest d. Regardless of laboratory values, hepatic decompensation diagnosed clinically – i. Changed to "New onset ascites **uncontrollable with diuretic**"	Changed to make the criteria clear and clinically reasonable.	• Clinical Protocol synopsis • Section 9.4.1.3.2 • Section 9.5.1.5.2
Add "Antiplatelet agents and anticoagulants that require INR monitoring" and "herbal supplements or alternative medicines" into **Prohibited**	Description Adjustment (corresponding to Section 9.4.7.2.1)	• Clinical Protocol synopsis

Concomitant Medications		
Update the introduction of pembrolizumab	Updated based on the latest pembrolizumab protocol standard text provided by Merck.	• Section 7.1.3
Update the information of the nonclinical study	Updated the information of the new nonclinical study of combination of lenvatinib plus anti-PD-1 mAb.	• Section 7.2.1 • Section 10
Update the information of the study E7080-G000-304 (Phase 3 of Lenvatinib Monotherapy for HCC)	Updated based on the news release by Eisai.	• Section 7.2.2.2
Update the information of the study E7080-J081-115 (Phase 1b of Lenvatinib Plus Pembrolizumab for Selected Solid Tumors in Japan)	Updated that the study is ongoing.	• Section 7.2.2.4
Update the language of completion of “The Discontinuation From Treatment CRF page”	Updated based on the latest protocol standard text of Eisai.	• Section 9.3.3
Update the language of reporting of “AEs leading screen failure”	Updated based on the latest protocol standard text of Eisai.	• Section 9.5.1.5.1
Add T3 or free T3 levels assessment at Screening and Baseline	Description Adjustment (corresponding to Inclusion criterion #12)	• Section 9.5.1.5.3 • Section 9.5.2.1
Add Child-Pugh score at each cycle Day1 and Off-Treatment Visit as well as Pre-treatment Phase	Added based on the necessity of data of Child-Pugh score.	• Section 9.5.2.1
Update the language of Subject Disposition CRF	Updated based on the latest protocol standard text of Eisai.	• Section 9.5.5

Summary of Changes

Revisions to Amendment 02

Date: 13 Jul 2017

Change	Rationale	Affected Protocol Sections
Add the language as follows; "For determination of the recommended phase 2 dose, all episodes of Grade 3 or 4 thrombocytopenia and neutropenia beyond Cycle 1 will be taken into consideration."	Added based on the FDA's feedback	• Clinical Protocol synopsis • Section 9.1
Revise the language for the DLT of "Hematologic" Toxicity Category so that the DLT criteria for thrombocytopenia is more conservative as follows; "Grade 4 thrombocytopenia lasting >/=7 days or Grade 3 thrombocytopenia associated with clinically significant hemorrhage or bleeding and/or requiring platelet transfusion"	Revised based on the FDA's feedback	• Clinical Protocol synopsis • Section 9.1
Revise the Exclusion Criterion#11 as follows so that patients with therapeutic anti-factor X treatment are excluded; "11.Bleeding or thrombotic disorders or use of factor X inhibitors or anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin is permitted. Antiplatelet agents are prohibited throughout the study. "	Revised based on the FDA's feedback	• Clinical Protocol synopsis • Section 9.3.2
Revise the language in "Prohibited Concomitant Medications" as follows; "Antiplatelet agents, factor X inhibitors, and anticoagulants that require INR monitoring, such as warfarin. (Treatments that do not require INR monitoring, such as low molecular weight heparin are	Revised based on the FDA's feedback	• Clinical Protocol synopsis • Section 9.4.7.2.1

Summary of Changes

Revisions to Amendment 02

Date: 13 Jul 2017

Change	Rationale	Affected Protocol Sections
permitted)"		
Add the language "Monitor subjects with Grade 4 thrombocytopenia every 48 hours until resolution to baseline or Grade 1."	Added based on the FDA's feedback	• Section 9.5.2.1

Summary of Changes

Revisions to Amendment 03

Date: 12 Feb 2018

Change	Rationale	Affected Protocol Sections
Add name and address of Eisai Ltd. as sponsor for the European Union (EU), and added EudraCT number to Title Page.	To accommodate opening of sites in the EU to enrollment.	• Section 1
Add KISPLYX® as the product name of lenvatinib	To accommodate opening of sites in the EU to enrollment.	• Section 1
Add IND number	Information of IND number is reflected.	• Section 1
Revise "Study Regions (Country) or Center"	To accommodate opening of sites in North America and Europe to enrollment in Expansion part.	• Clinical Protocol synopsis • Section 6
Add the following language into Primary Objectives; "(Expansion part) To evaluate objective response rate (ORR) and duration of response (DOR) by modified Response Evaluation Criteria In Solid Tumors for HCC (mRECIST) and RECIST 1.1 based on independent imaging review (IIR)".	Revised the Primary Objectives to add ORR and DOR by mRECIST and RECIST1.1 based on IIR in Expansion part, considering the importance and necessity of these efficacy endpoints in Expansion part.	• Clinical Protocol synopsis • Section 7 • Section 8.1
Revise the languages for ORR /DOR of DLT evaluation Part, and for ORR/DOR of Expansion Part by mRECIST based on investigator review in Secondary Objectives	Description adjustment to clarify that they are Secondary Objectives.	• Clinical Protocol synopsis • Section 8.2
Delete PFS, TTP, TTR and OS from Exploratory Objectives and add them into Secondary Objectives	Transferred PFS, TTP, TTR and OS from Exploratory Objectives to Secondary Objectives, considering the importance of these efficacy endpoints.	• Clinical Protocol synopsis • Section 8.2 • Section 8.3
Delete to evaluate the efficacy endpoints and assessments by irRECIST and irmRECIST (optional, Expansion Part) and delete it from Exploratory Objectives	Deleted the related languages, considering the necessity of these efficacy endpoints.	• Clinical Protocol synopsis • Section 8.3 • Section 9.5.1.3
Add to evaluate HRQoL using EORTC QLQ-C30, QLQ-	Added them into Exploratory Objectives considering the	• Clinical Protocol synopsis • Section 8.3

Summary of Changes

Revisions to Amendment 03

Date: 12 Feb 2018

Change	Rationale	Affected Protocol Sections
HCC18 and EQ-5D-5L for the subjects in Expansion Part added as of the Protocol Amendment 03, and add the languages into Exploratory Objectives, Study Endpoints and Assessments	necessity of the endpoint.	• Section 9.5.1.6
Add the option to increase enrollment in Expansion part to up to approximately 94 subjects based on the results of 2 interim analyses after 20 and 56 subjects have sufficient follow-up to be evaluated for response, and revise Sample Size Rationale in alignment with this revision	To obtain additional efficacy and safety data for the combination in Expansion part based on clinical results.	• Clinical Protocol synopsis • Section 9.1 • Section 9.3 • Section 9.7.2 • Section 9.7.3
Add the following language to Inclusion Criterion#12; "As of Amendment 03, subjects with T3, free T3 or free T4 abnormalities at screening who are asymptomatic can be eligible"	Changed to make the criterion more clinically reasonable.	• Clinical Protocol synopsis • Section 9.3.1
Revise the language for Exclusion Criterion #15 as follows; "Active infection (any infection requiring systemic treatment). Hepatitis B or C [HBV/HCV] is allowed."	Revised to make the language clear.	• Clinical Protocol synopsis • Section 9.3.2
Revise the language of Exclusion Criterion#20 as "Change to "Subjects with CNS metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study	Revised based on the standard language of lenvatinib.	• Clinical Protocol synopsis • Section 9.3.2

Summary of Changes

Revisions to Amendment 03

Date: 12 Feb 2018

Change	Rationale	Affected Protocol Sections
treatment."		
Delete the following Exclusion Criterion #26; "Subjects being treated with drugs that strongly inhibit or induce CYP3A4 and that may be possibly used during this study"	Deleted since the criterion is no longer necessary for the subjects in Expansion part added as of Protocol Amendment 03.	• Clinical Protocol synopsis • Section 9.3.2
Revise the language of footnote b of Lenvatinib Dose Reduction and Interruption Instructions	Revised based on the standard language of lenvatinib.	• Clinical Protocol synopsis • Section 9.4.1.3.2
Update "Dose Interval Modification Guidelines for Non-Hepatic Drug-Related Adverse Events Associated with Pembrolizumab"	Updated based on the latest pembrolizumab protocol standard text provided by Merck.	• Clinical Protocol synopsis • Section 9.4.1.3.2
Update "Guidance for Management of Hepatic Events of Clinical Interest" and related languages including "Permanent Discontinuation Criteria for Subjects With Non-overdose Hepatic Events of Clinical Interest" and "Diagnosis and Management of Non-Overdose Hepatic Events of Clinical Interests"	Updated to make the language clear and clinically reasonable based on the discussion with Merck.	• Clinical Protocol synopsis • Section 9.4.1.3.2 • Section 9.5.1.5.2
Add the language to clarify that images acquired for tumor assessments both in DLT evaluation part and Expansion part will be sent to an ICL for archiving and independent analysis	Added considering the necessity of IIR of tumor assessments in DLT evaluation part as well as Expansion part.	• Clinical Protocol synopsis • Section 9.5.1.3
Delete $ORR_{(week24)}$ from study endpoints and analysis	Deleted the related languages, considering the necessity of the endpoint.	• Clinical Protocol synopsis • Section 9.7.1.1.3 • Section 9.7.1.6
Add the expected study duration	Added as required by some regulatory agencies	• Section 5.1 • Section 9.1
Add the following languages: "European Good Clinical Practice Directive 2005/28/EC	To accommodate opening of sites in the EU to enrollment.	• Section 5.2

Summary of Changes

Revisions to Amendment 03

Date: 12 Feb 2018

Change	Rationale	Affected Protocol Sections
and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states."		
Revise "Management of Hypertension" and "Management of Proteinuria" in "Supportive Care Guidelines for Lenvatinib"	Revised based on the standard language of lenvatinib.	• Section 9.4.1.4.1 • Section 9.4.1.4.2
Revise the language of "Rescue Medications and Supportive Care for Pembrolizumab" including "Infusion Reaction Treatment Guidelines"	Updated based on the pembrolizumab protocol standard text provided by Merck.	• Section 9.4.1.5
Revise the language of "Prohibited Concomitant Medications"	Updated to make the language clear regarding concomitant medications which are allowed.	• Section 9.4.7.2.1
Add the following language: "Discontinuation of pembrolizumab treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab beyond the date when the initial CR was declared."	Updated based on the pembrolizumab protocol standard text provided by Merck.	• Section 9.5.1.3
Add the sparse sampling scheme of collecting blood samples for lenvatinib pharmacokinetic assessments for the subjects in Expansion part added as Protocol Amendment 03	Added the language considering that the sparse sampling scheme is reasonable for the subjects in Expansion part added as this Protocol Amendment.	• Section 9.5.1.4.1
Add urine protein-to-creatinine ratio (UPCR) into Clinical Laboratory Tests as optional measurement	Added based on the revision of "Management of Proteinuria" in "Supportive Care Guidelines for Lenvatinib"	• Section 9.5.1.5.3

Summary of Changes

Revisions to Amendment 03

Date: 12 Feb 2018

Change	Rationale	Affected Protocol Sections
Revise the language of "Vital Signs and Weight Measurements" particularly regarding measurements and assessments of blood pressure	Updated based on the revision of "Management of Hypertension" in "Supportive Care Guidelines for Lenvatinib"	• Section 9.5.1.5.4
Update the Schedule of Procedures/Assessments	Added assessments of HRQoL and lenvatinib PK blood samples for the subjects in Expansion part added as of this Amendment.	• Section 9.5.2.1
Update Study Endpoints based on the changes of Study Objectives	Updated primary endpoints, secondary endpoints and exploratory endpoints based on the revision of Study Objectives (Section 8).	• Section 9.7.1.1
Updated Reference list	Description adjustment	• Section 10
Update KEYTRUDA® Package Insert and Summary of Product Characteristics	To include updated information	• Appendix 11

Summary of Changes

Revisions to Amendment 04

Date: 13 Aug 2018

Change	Rationale	Affected Protocol Sections
Add reference to main protocol section on supportive care guidelines in the synopsis.	To provide specific location of supportive care guidelines in the main protocol.	• Clinical Protocol Synopsis
Added symbol "≤" to specify acceptable blood pressure for inclusion criterion 7.	Clarification per request from AEMPS.	• Clinical Protocol Synopsis • Section 9.3.1
Add hypersensitivity to lenvatinib and/or any of its excipients to exclusion criterion 31.	Added as per MHRA request.	• Clinical Protocol Synopsis • Section 9.3.2
Added exclusion criterion 32, "any subjects with non-GI fistula."	Added as per ANSM request.	• Clinical Protocol Synopsis • Section 9.3.2
Added a statement that subjects who stop study treatment after receiving 35 administrations of pembrolizumab (approximately 2 years) for reasons other than progressive disease or intolerability, or subjects who attain a complete response and stop study treatment, may be eligible to receive a second course of treatment of up to 17 additional administrations of pembrolizumab (approximately 1 year).	Added as per ANSM request.	• Clinical Protocol Synopsis • Section 9.4.1.2 • Section 9.5.2.1 (Table 9, footnote "dd")
Added sections 9.1.4 and 9.5.1.3.1. Added Table 10 in section 9.5.2.1, schedule of procedures/assessments in the second course of treatment.	To describe conditions for the second course of treatment with pembrolizumab.	• Clinical Protocol Synopsis • Section 9.1.4 • Section 9.5.1.3.1 • Section 9.5.2.1

Added footnote “i” to Table 2, indicating that Grade 4 is applicable to hematologic toxicities only, not to proteinuria.	Per ANSM request, Table 2 has been clarified with an additional footnote so that Grade 4 is applicable to hematologic toxicities only. This is because Grade 4 proteinuria does not exist in the CTCAE classification.	• Clinical Protocol Synopsis • Section 9.4.1.3.2
In the event of first recurrence Grade 3 colitis, pembrolizumab treatment is to be permanently discontinued.	Added as per ANSM request.	• Clinical Protocol Synopsis • Section 9.4.1.3.2
Updated information for Study E7080-G000-304.	Study was completed.	• Section 7.2.2.2
Request a discussion with sponsor in case investigator is considering starting HCV anti-viral therapy.	Added in response to ANSM. The language is consistent with other pembrolizumab protocols in the same indication.	• Section 9.4.1.3.2
Add treatment discontinuation in case of nephrotic syndrome.	Added as per MHRA request.	• Section 9.4.1.4.2
Add treatment discontinuation in case of any grade of arterial thromboembolism.	Added as per MHRA request.	• Section 9.4.1.4.4
Tables 8 and 9 have been amended to more clearly reflect the protocol's requirement for a pregnancy test either monthly, or before each administration of pembrolizumab.	Clarification has been added per ANSM request.	• Section 9.5.1.5.3 • Section 9.5.2.1

Summary of Changes

Revisions to Amendment 05

Date: 17 Jan 2019

Change	Rationale	Affected Protocol Sections
Exclusion criterion #27 updated to allow use of systemic steroids up to 10 mg/d of prednisone.	Changed to clarify the physiologic dose of prednisone.	• Synopsis • Section 9.3.2
The Follow-up Period for collecting SAE data was changed from 90 days to 120 days.	Changed to be consistent with other protocols in the lenvatinib + pembrolizumab development program.	• Synopsis • Section 9.5.1.5.1 • Section 9.5.4.1
Added "(date of first study dose)" to the OS endpoint description.	Clarified timing to be consistent with description of other endpoints.	• Synopsis • Section 9.7.1.1.2
Added "at least" to the data cutoff date for the primary analysis to clarify the minimal time allowed for the duration of follow up.	Changed to clarify the data cutoff for the primary analysis to be done.	• Synopsis • Section 9.7.1.6
RECIST 1.1 changed to mRECIST.	Corrected to show that the investigator assessment is performed using mRECIST.	• Section 9.1.4
Table 6 modified to clarify subject's blood samples for PK assessments.	Clarified to be consistent with protocol text.	• Section 9.5.1.4.1
Table 10 and table footnotes corrected to more clearly reflect the main text of the protocol.	Made consistent with the main text of the protocol.	• Section 9.5.2.1

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 Hepatocellular Carcinoma

Study Regions (Country) or Center

DLT evaluation part: Two centers in Japan

Expansion Part: multiple centers in Japan, North America, and Europe

Study Period and Phase of Development

Approximately 30 months

Phase 1b

Objectives

Primary Objectives

- To evaluate the tolerability and safety for combination of lenvatinib plus pembrolizumab in subjects with hepatocellular carcinoma (HCC)
- (Expansion part) To evaluate objective response rate (ORR) and duration of response (DOR) by modified Response Evaluation Criteria In Solid Tumors for HCC (mRECIST) and RECIST 1.1 based on independent imaging review (IIR)

Secondary Objectives

- (DLT evaluation Part) To evaluate ORR and DOR by mRECIST (based on investigator review and IIR), and by RECIST1.1 based on IIR
- (Expansion Part) To evaluate ORR and DOR by mRECIST based on investigator review
- To evaluate the following efficacy endpoints by mRECIST (based on investigator review and IIR) and RECIST1.1 (based on IIR) :
  - Progression-free survival (PFS)
  - Time to progression (TTP)
  - Time to response (TTR)
- Overall survival (OS)
- 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 mRECIST (based on investigator review and IIR) and RECIST1.1 (based on IIR) :
  - Disease control rate (DCR)
  - Clinical benefit rate (CBR)
- To evaluate the impact of treatment on Health Related Quality of Life (HRQoL) for subjects treated using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, HCC-specific EORTC QLQ-HCC18 questionnaire and European Quality of Life

questionnaire.

For the subjects in Expansion part added as of the protocol Amendment 03, HRQoL will be evaluated using the EORTC QLQ-C30 and the HCC specific supplement QLQ-HCC18. HRQoL will also be evaluated using the generic EuroQuol five dimension five level (EQ-5D-5L) questionnaire.

- 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 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 evaluate the tolerability and safety of lenvatinib in combination with pembrolizumab in subjects with HCC.

This study will begin with lenvatinib 12 mg (Body Weight [BW] ≥60 kg) or 8 mg (BW <60 kg) /day orally and pembrolizumab 200 mg (every 3 weeks [Q3W], intravenous [IV]) in subjects with HCC. Tolerability of this dose level will be evaluated by dose-limiting toxicities (DLTs) during the first cycle (21-day treatment cycle).

In this dose level, 3 subjects will be enrolled first. If 0 or 1 of 3 subjects in a given dose level cohort experiences a DLT, then 3 more subjects will be enrolled into that dose level. If 0 or 1 of 6 subjects in a given dose level cohort experiences a DLT, the dose level will be considered tolerable. Additional 4 subjects can be enrolled without DLT evaluation if further safety information is considered necessary based on the discussions between the sponsor and investigators.

Enrollment will be interrupted if 2 or more DLTs are observed in this 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, after sponsor and investigators' review regarding the nature and severity of the DLTs, an additional 4 subjects (10 subjects in total for DLT evaluation) will be enrolled, and that dose level will be considered to be tolerable if DLT is observed in 3 or less of the 10 subjects in total. An independent medical advisor as third party may be consulted for the review as needed.

In this dose level, at least 3 subjects treated with lenvatinib 12 mg once daily (QD) and pembrolizumab 200 mg Q3W IV (BW ≥60 kg) need to be included in the 6 subjects for DLT evaluation. (In case of the 10 subjects for DLT evaluation, at least 5 subjects (BW ≥60 kg) treated with lenvatinib 12 mg QD and pembrolizumab 200 mg Q3W IV need to be included.)

Cohort of reduction to lower dose level (lenvatinib) or study discontinuation will be considered, if this dose level (12 mg [BW ≥60 kg] or 8 mg [BW <60 kg] lenvatinib plus 200 mg pembrolizumab) 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 maybe 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.

For determination of the recommended phase 2 dose, all episodes of Grade 3 or 4

thrombocytopenia and neutropenia beyond Cycle 1 will be taken into consideration.

If the dose level is confirmed to be tolerable, an additional (approximately) 20 subjects will be enrolled for consolidation of PK data and safety and efficacy as the **Expansion part**. As of Amendment 03, the Expansion part may be further expanded up to approximately 94 subjects. The decision to expand enrollment will be based on the results of 2 interim analyses that will take place when 20 (6 subjects for DLT evaluation part plus 14 subjects for Expansion part) and 56 subjects (6 subjects for DLT evaluation part plus 50 subjects for Expansion part) have sufficient follow-up to be evaluated for response. The decision to expand enrollment will be assessed by mRECIST based on investigator review. At the first interim analysis (N = 20), if there are more than 5 responses, then approximately 36 additional subjects will be enrolled. At the second interim analysis (N = 56), if there are more than 16 responses, approximately 44 additional subjects will be enrolled. If there are 5 or fewer responses at the first interim analysis (N = 20) or 16 or fewer responses at the second interim analysis (N=56), the sponsor may decide whether to expand enrollment based on other clinical outcome (eg, DOR). At least 5 subjects (BW ≥60 kg) treated with Lenvatinib 12 mg QD and at least 5 subjects (BW <60 kg) treated with Lenvatinib 8 mg QD will be included in Expansion part.

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 week 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 above febrile neutropenia
	Grade 4 thrombocytopenia lasting ≥7 days or Grade 3 thrombocytopenia associated with clinically significant hemorrhage or bleeding and/or requiring platelet transfusion
Nonhematologic toxicity	Grade 4 or 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 gastrointestinal perforation
	Grade 3 wound dehiscence requiring medical or surgical intervention
	Grade 3 thromboembolic event
	Any Grade 3 nonhematologic laboratory value (except AST/ALT) if:

	Medical intervention is required to treat the subject, or the abnormality leads to hospitalization Note: Abnormal laboratory values to which treatment and hospitalization is not required can be deemed a non-DLT
	AST/ALT >10.0×ULN, which does not resolve within 1 week, or else is clinically symptomatic.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events v4.03, DLT = dose-limiting toxicity, ULN = upper limit of normal.

Adverse events (AEs) with a clear alternative explanation (eg, due to disease progression) 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 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 and the Follow-up. The Off-Tx Visit will occur within 30 days following the last dose of study treatment. Following the completion of the Off-Tx Visit, subjects will transition to the Follow-up. The Follow-up will continue as long as the study subject is alive unless the subject withdraws consent or until the sponsor terminates the study. In the Follow-up, subjects will be treated by the investigator according to the prevailing local standard of care. For survival and subsequent anticancer treatments, subjects will be followed every 12 weeks (±1 week) or at sponsor's request. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email. The survival follow-up will be continued for up to 2 years after Cycle 1/Day 1 (C1D1) of the last subject enrolled in the Expansion part. The sponsor may decide to terminate survival follow-up anytime during the Extension Phase or when all subjects have discontinued study treatment. All AEs will be captured for 30 days after the last dose of study drug. Serious AEs regardless of causality assessment must be collected through the last visit and for 120 days after the subject's last dose or for 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier.

Second Course (Pembrolizumab Retreatment) Phase: Subjects who stop study treatment after receiving 35 administrations of pembrolizumab for reasons other than progressive disease (PD) or intolerability, or subjects who attain a complete response (CR) and stop study treatment, may be eligible to receive a second course of treatment of up to 17 additional administrations of

pembrolizumab (approximately 1 year).

Number of Subjects

This study will enroll approximately 30 evaluable subjects with HCC (N=6 to 10 for DLT evaluation part and N=20 for Expansion part). As of Amendment 03 the enrollment for Expansion part may be further expanded up to approximately 94 evaluable subjects.

Inclusion Criteria

1. Subjects must have confirmed diagnosis of HCC with any of the following criteria:
   - Histologically or cytologically confirmed diagnosis of HCC, excluding fibrolamellar, sarcomatoid or mixed cholangio-HCC tumors
   - Clinically confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases (AASLD) criteria, including cirrhosis of any etiology and/or chronic hepatitis B or C infection
2. HCC for which no other appropriate therapy is available

   Note: Subjects basically should receive prior standard therapy including sorafenib. However, if the investigator judges the therapy is not appropriate for the subject, the prior standard therapy is not necessarily mandated for the eligibility.

   Expansion Part: No prior systemic therapy for advanced/unresectable HCC

   Note: Subjects who have received local hepatic injection chemotherapy are eligible.
3. Subjects categorized to stage B (not applicable for transarterial chemoembolization [TACE]), or stage C based on Barcelona Clinic Liver Cancer (BCLC) staging system
4. At least 1 measurable target lesion according to mRECIST meeting the following criteria.
   - Hepatic lesion
     i. The lesion can be accurately measured in at least 1 dimension as ≥1.0 cm (viable tumor for typical; and longest diameter for atypical), and
     ii. The lesion is suitable for repeat measurement
   - Nonhepatic lesion
     i. Lymph node (LN) lesion that measures at least 1 dimension ≥1.5 cm in the short axis, except for porta hepatis LN that measures ≥2.0 cm in the short axis
     ii. Non-nodal lesion that measures ≥1.0 cm in the longest diameter

   Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression to be deemed a target lesion. Subjects whose only target lesion(s) is in bone will be excluded.
5. Child-Pugh score A
6. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1
7. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week prior to the C1D1
8. 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
9. Adequate bone marrow function:

- Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5×10^3/μL)
- Platelets ≥75,000/mm^3 (≥75×10^9/L)
- Hemoglobin ≥8.5 g/dL

10. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤2.3
11. Adequate liver function, defined as:
    - Bilirubin ≤2.0 mg/dL
    - Aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) ≤5×ULN
12. Total triiodothyronine (T3) or free T3 and free thyroxine (T4) are within normal limits. (control by thyroid replacement therapy is acceptable.) As of Amendment 03, subjects with T3, free T3 or free T4 abnormalities at screening who are asymptomatic can be eligible.
13. Males or females age ≥18 years at the time of informed consent
14. Life expectancy of 12 weeks or more
15. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol
16. **Expansion Part**: Archival tumor tissue or a newly obtained biopsy must be available prior to the first dose of study drug for biomarker analysis.
    - Subjects without archival tumor tissue and with inaccessible tumors for biopsy specimens can be enrolled without a biopsy.
    - 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.

    Note: Collection of archival tumor tissue or a newly obtained biopsy prior to the first dose of study treatment will be optional in the patients who are not enrolled in Expansion cohort.

Exclusion Criteria

1. Imaging findings for HCC corresponding to any of the following:
    - HCC with ≥50% liver occupation
    - Clear invasion into the bile duct
    - Portal vein invasion with Vp4
2. Prior anticancer treatment within 28 days (or within 14 days in case of sorafenib) 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 and controlled stable cases).
   Note: Refer to inclusion criteria regarding hypertension.
3. Any blood enhancing treatment (including blood transfusion, blood products, or agents that stimulate blood cell production, eg, granulocyte colony-stimulating factor [G-CSF]) within 28 days prior to the first dose of study drugs
4. Prior treatment with lenvatinib or any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent
5. Subjects must have recovered adequately from any complications from major surgery prior to starting therapy.
6. 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.

7. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib
8. 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
9. Prolongation of QTc (Fridericia formula) interval to >480 ms
10. Gastrointestinal bleeding event or active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug
11. Bleeding or thrombotic disorders or use of factor X inhibitors or anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin is permitted. Antiplatelet agents are prohibited throughout the study.
12. Gastric or esophageal varices that require interventional treatment within 28 days prior to first dose of study drug are excluded. Prophylaxis with pharmacologic therapy (eg, nonselective beta-blocker) is permitted.
13. Surgical arterial-portal venous shunt or arterial-venous shunt
14. Active malignancy (except for HCC or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 36 months
15. Active infection (any infection requiring systemic treatment). Hepatitis B or C [HBV/HCV] is allowed.
16. In case of HBsAg (+) subjects: Antiviral therapy for HBV must be given for at least 3 months prior to first dose of study drug, and HBV viral load must be less than 100 IU/mL prior to first dose of study drug.
    - Subjects who are HBsAg (+) and on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment.
    - Subjects without HBV prophylaxis who are anti-HBcAb (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA do not require prophylaxis
    - Subjects with HBV prophylaxis who are anti-HBcAb (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA should continue the prophylaxis.
    - In all the subjects above, they need monitoring with HBV DNA every 3 weeks during the study treatment.
17. Therapy for HCV must be completed at least 4 weeks prior to first dose of study drug in case of Hepatitis C subjects who are on active HCV treatment. Hepatitis C subjects who are untreated or uncured may also be enrolled.
18. Has dual active HBV infection (HBsAg (+) and /or detectable HBV DNA) and HCV infection (anti-HCV Ab(+) and detectable HCV RNA) at study entry.
19. Meningeal carcinomatosis
20. Subjects with CNS metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
21. Subject is known to be positive for Human Immunodeficiency Virus (HIV).

22. History of clinically significant hepatic encephalopathy
23. Serious nonhealing wound, ulcer, or bone fracture
24. History of solid organ or hematologic transplant
25. Any subject who cannot be evaluated by either triphasic liver computed tomography (CT) or triphasic liver magnetic resonance imaging (MRI) because of allergy or other contraindication to both CT and MRI contrast agents
26. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial
27. 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 10 mg/d of prednisone or equivalent) may be approved after consultation with the sponsor. The use of steroids in prophylaxis of allergic reaction by CT contrast agents will be allowed.
28. 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.
29. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis, or has a history of interstitial lung disease.
30. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
31. Has severe hypersensitivity (≥ Grade 3) to pembrolizumab or lenvatinib and/or any of their excipients.
32. Any subjects with non-GI fistula.
33. Subjects who meet any of the following criteria will be excluded from this study:
    1) 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.
    2) 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 [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing]

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

34. 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 #32) 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 capsule. 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 for up to 2 years after C1D1 at the longest. Subjects who stop study treatment after receiving 35 administrations of pembrolizumab for reasons other than progressive disease (PD) or intolerability, or subjects who attain a complete response (CR) and stop study treatment, may be eligible to receive a second course of treatment of up to 17 additional administrations of pembrolizumab (approximately 1 year).

Study Treatment Dose Modification

1. Cycle 1 (except for Expansion part)

a. If DLT occurs:

Lenvatinib and infusion of pembrolizumab should be interrupted immediately. Treatment may be resumed in Cycle 2 of pembrolizumab (except for toxicity which requires permanent discontinuation according to the guidance) and at 1 lower dose level of lenvatinib if toxicity is resolved to Grade 0–1 (or tolerable Grade 2 for Hematologic Toxicities and Proteinuria in case of

lenvatinib treatment-related toxicity) or baseline and investigators decide 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 (and applies to Cycle 1 and onward of Expansion part)

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.

See Section 9.4.1.4 of the main protocol for supportive care guidelines, including the management of hypertension and proteinuria, 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.

Starting dose of lenvatinib will be based on baseline BW as follows:

- BW ≥60 kg — 12 mg QD. Study subjects will be orally administered lenvatinib as three 4-mg capsules
- BW <60 kg — 8 mg QD. Study subjects will be orally administered lenvatinib as two 4-mg capsules

Dose adjustments for management of intolerable toxicities will be made according to the guidelines provided in the table below.

Lenvatinib Dose Reduction and Interruption Instructions

Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QOD]). Any dose reduction below 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.

Nonhematologic Toxicities		
Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment[c]	No change
Intolerable Grade 2[c] or Grade 3[d,e,h]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 more dose level
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4[g,h]: Discontinue Lenvatinib		

Hematologic Toxicities and Proteinuria		
Treatment-Related Toxicity[a]	**Management**	**Dose Adjustment**
Grade 1 or Grade 2[e]		

	Continue treatment[c]	No change
Grade 3[e]		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	No change
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 dose level
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence [f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fifth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discuss with sponsor
Grade 4[i]		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discuss with sponsor

Note: Grading according to CTCAE v4.03.
AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, γ-GTP = γ-glutamyltransferase, CTCAE v4.03 = Common Terminology Criteria for Adverse Events Version 4.03, Na = sodium, ULN = upper limit of normal, QD = once daily.

a: An interruption of lenvatinib for more than 21 days (due to lenvatinib treatment-related toxicities) will require sponsor's approval before treatment can be resumed. During treatment interruption, repeat AEs assessment at least every 7 days (until restarting administration).
b: Excluding alopecia. Initiate optimal medical management for nausea, vomiting, diarrhea, and/or hypothyroidism prior to any lenvatinib treatment, interruption, or dose reduction. For treatment-related hypertension, refer to Management of Hypertension (Section 9.4.1.4.1) for dose modification guidelines.
c: Grade 2 toxicities will be determined to be tolerable or intolerable by both the subject and investigator. If Grade 2 toxicity is determined to be intolerable, the dose of study drug will be reduced with or without dose interruption. Interruption for Grade 3 toxicities is mandatory.
d: Obese subjects with weight loss do not need to return to baseline or Grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least 1 week, and subjects should be started at the lower dose and normal BMI should be used for future dose reductions.
e: Not applicable to abnormal clinical laboratory values that are not clinically relevant based on the judgment of the investigator (eg, ALT, AST, γ-GTP values <10×ULN, and Na).
f: Not applicable for subjects who start at 8 mg QD.
g: Excluding laboratory abnormalities judged to be nonlife-threatening, which should be managed as Grade 3.
h: For asymptomatic Grade ≥3 elevations of amylase and lipase, sponsor should be consulted to obtain permission to continue treatment.
i: Only applicable to Hematologic Toxicities.

Dose Reduction for Lenvatinib Treatment-Related Toxicity Initial Lenvatinib Dose (mg, QD)	**Adjusted Dose To Be Administered (mg, QD)**		
	Reduction 1	**Reduction 2**	**Reduction 3**
12	8	4	4[a]
8	4	4[a]	

QD = once daily.

a: 4 mg every other day [QOD]. Any dose reduction below 4 mg every other day must be discussed with the sponsor.

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.

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

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 regarding non-hepatic drug-related AEs or the following guidance for hepatic events of clinical interest. See Section 9.4.1.5 for supportive care guidelines, including use of corticosteroids, and **Guidance for Management of Hepatic Events of Clinical Interest** below for dose modification and management of hepatic events of clinical interest.

Dose Interval Modification Guidelines for Non-Hepatic Drug-Related Adverse Events Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3	Permanently discontinue at the first recurrence of Grade 3 colitis		
	Grade 4	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.

	associated with evidence of β-cell failure		participants with hyperglycemia	
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not		

		limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

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

See Table 5 for Infusion Reaction Treatment Guidelines in Section 9.4.1.5 for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Dosing interruptions are permitted in the case of medical/surgical events or for 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.

Guidance for Management of Hepatic Events of Clinical Interest

Hepatic events of clinical interest will include any of the following events. All of these events will require holding pembrolizumab treatment. All cases of retreatment and permanent discontinuation must be reported to the sponsor. Refer to Protocol for further details.

a. ALT:
   i. Among subjects with baseline ALT <2×ULN: ALT ≥5×ULN
   ii. Among subjects with baseline ALT ≥2×ULN: ALT >3× the Baseline level
   iii. ALT >500 U/L regardless of baseline level

b. AST:
   i. Among subjects with baseline AST <2×ULN: AST ≥5×ULN
   ii. Among subjects with baseline AST ≥2×ULN: AST >3× the Baseline level
   iii. AST >500 U/L regardless of baseline level

c. Total Bilirubin:
   i. Among subjects with baseline levels <1.5 mg/dL: a value of >2.0 mg/dL
   ii. Among subjects with baseline levels that are ≥1.5 mg/dL: a value ≥2× the baseline level
   iii. Total bilirubin >3.0 mg/dL regardless of baseline level

d. Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
   i. New onset ascites uncontrollable with diuretic
   ii. Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)
   iii. Hepatic Encephalopathy

Note: See Immediate Assessment of Section 9.4.1.3.2.

Permanent Discontinuation Criteria for Subjects With Non-overdose Hepatic Events of Clinical Interest

Pembrolizumab should also be permanently discontinued for:

- ALT >20×ULN
- Child-Pugh (CP) score of ≥9 points
- Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)[a]
- Hepatic Encephalopathy[a]
- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related.

a: Pembrolizumab is not necessarily discontinued if it is judged by Investigator that the AE is not associated with pembrolizumab (eg, lenvatinib treatment-related toxicity) after discussion with sponsor.

Other subjects may be eligible for treatment interruption (and potential re-start) of pembrolizumab after discussion with the sponsor.

See **Diagnosis and Management of Non-Overdose Hepatic Events of Clinical Interests** of Section 9.4.1.3.2 for management details of **hepatitis B flare, hepatitis C recurrence or flare, immune-related hepatitis, and other hepatic events of clinical interest**.

Duration of Study

Study duration for each subject is estimated to be:

- **Pretreatment Phase**: 4 weeks
- **Treatment Phase**: 3 weeks (1 cycle)
- **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 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 this study:

- Anticancer therapies such as chemotherapy, tyrosine kinase inhibitors (TKIs), local therapy, antitumor interventions (surgical resection, thoracocentesis, etc.), or immunotherapy other than study drugs
- 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.
- 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. The use of steroids in prophylaxis of allergic reaction by CT contrast agents will be allowed.
- Antiplatelet agents, factor X inhibitors, and anticoagulants that require INR monitoring, such as warfarin. (Treatments that do not require INR monitoring, such as low molecular weight

heparin are permitted.)

- No herbal supplements or alternative medicines are allowed during this study.

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. See the related Exclusion Criteria regarding antiviral therapy for HBV and HCV.

Assessments

Efficacy

Tumor assessments will be performed by the investigators using **mRECIST for HCC** (Lencioni and Llovet, 2010). All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans from subjects for DLT evaluation must be accessible in the event of a sponsor request to submit them for central review. For the Expansion part, images acquired for tumor assessments will be sent to an imaging core laboratory (ICL) for archiving and potential independent analysis including **RECIST 1.1** (Eisenhauer, et al., 2009), and mRECIST for HCC. As of Amendment 03, images acquired for tumor assessments both in DLT evaluation part and Expansion part will be sent to an ICL for archiving and independent analysis.

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

Screening tumor assessments using triphasic liver CT/MRI (optimized for pre-contrast, arterial, and portal venous phase), contrast-enhanced CT of the chest, and contrast-enhanced CT or MRI of abdomen, pelvis, and other areas of known disease plus suspected disease should be performed within 28 days prior to C1D1.

Screening CT of the brain with contrast or MRI of the brain pre- and post-gadolinium should be performed within 28 days prior to C1D1. During the Treatment Phase and the Extension Phase, CT/MRI of the brain should be performed if clinically indicated. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability.

During the Treatment Phase and Extension Phase, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease at Screening plus newly suspected disease should be performed every 6 weeks (±1 week, starting from the date of C1D1) until Week 24 and every 9 weeks thereafter, or sooner, if clinically indicated. The same methodology (CT or MRI) and scan acquisition techniques including use and timing of IV contrast should be used as for the screening assessments. Tumor assessment at the Off-Tx Visit is only necessary if more than 4 weeks have passed since the previous assessment (window for these assessments is within 1 week of the Off-Tx Visit).

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.

All subjects are required to undergo chest, abdomen, and pelvis imaging at baseline and at all follow-up time points. Contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis, and any other areas of disease, as clinically indicated, will be acquired at Screening and at all imaging time points. Liver CT or MRI must be performed using triphasic scanning technique optimized to capture pre-contrast, arterial, and portal venous phase. Contrast-enhanced CT or MRI (pre-and post-gadolinium) of the brain will be acquired at Screening and as clinically indicated.

Treatment decisions by the investigator will be based on mRECIST for HCC. If the time point tumor assessment is progressive disease (PD) per mRECIST, the investigator will consider whether the subjects should discontinue from study treatment. The decision to continue study treatment after the initial progression per mRECIST is at the investigator's discretion based on the clinical status of the subject. Subjects will be considered to discontinue study treatment upon evidence of further radiologic progression as judged by the investigator. However, subjects will be permitted to continue treatment beyond initial progression per mRECIST as long as the investigator judges that the subject is clinically stable and still receiving clinical benefit and is tolerating study drug treatment. Clinically stable is 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

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

In order for stable disease (SD) 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 of (partial response [PR] or complete response [CR]) should be confirmed no less than 4 weeks after the initial response, but generally at the next scheduled tumor assessment time point.

Pharmacokinetic

Plasma concentrations of lenvatinib and serum concentrations of pembrolizumab will be measured, and serum ADA will also be 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, on Cycle 1/Day 15 (C1D15), and predose on Day 1 of subsequent cycles up to and including Cycle 18, and at the off-treatment assessment. Subjects will provide an archival tumor tissue sample and/or a fresh biopsy of tumor before treatment for biomarker analyses (see the Inclusion Criteria). 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-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 tumor biopsies will be collected from consented subjects to examine markers including markers of target engagement, relevant pharmacodynamic biomarkers, and potential markers of response.

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 predose on C1D15 and Day 1 of subsequent cycles up to and including Cycle 18 and at the off-treatment assessment. Cf-nucleic acids 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.

Data will be used to explore pharmacokinetics/pharmacodynamic (PK/PD) relationships for effects of lenvatinib in combination with pembrolizumab on ORR, other efficacy-related parameters including PFS and OS, AEs/dose reductions, and blood-borne and tumor biomarkers. Exploratory/graphical analyses will be conducted for PK/PD evaluations and may be followed by model-based analyses. PK/PD results will be provided in a separate report.

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

Safety

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (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).

Other Assessments

For the subjects in Expansion part added as of Protocol Amendment 03, assessments of HRQoL scores will be performed using the generic cancer HRQoL instrument (EORTC QLQ-C30), the HCC-specific module (EORTC QLQ-HCC18), and the generic HRQoL instrument, EQ 5D-5L. Subjects will be asked to complete each of the three questionnaires at the Baseline Visit, on Day 1 of each subsequent cycle, and at the Off-Treatment Visit. Validated translations of questionnaires will be used according to EORTC and FDA guidelines.

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 based on mRECIST and RECIST 1.1 except for OS.

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

DOR is defined as the time from the first documentation of CR or PR to the date of first documentation of disease progression 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 or death (whichever occurs first).

TTP is defined as the time from the first study dose date to the date of first documentation of disease progression.

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

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

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

OS is measured from the start date of the Treatment Phase (date of first study dose) until date of death from any cause. Subjects who are lost to follow-up and the subjects who are alive at the date of data cutoff will be censored at the date the subject was last known alive or the cut-off date, whichever comes earlier.

As Exploratory Endpoints, HRQoL will be assessed using EORTC QLQ-C30 and the HCC-specific supplemental questionnaire (HCC-18) for the subjects in Expansion part added as of Protocol Amendment 03. The generic EQ-5D-5L will be used for the expanded subjects added as of Protocol Amendment 03.

Analysis Sets

DLT Analysis Set will include all subjects (except for the Expansion part) 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 determine 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 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, OS, TTP 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 post-baseline nadir (ie, maximum tumor shrinkage).

Data cutoff for the primary analysis will be done after all subjects in the Expansion part finish at least Cycle 8 assessment and have a tumor assessment for at least Week 24, or discontinue if before Cycle 8.

Pharmacokinetic and/or Pharmacodynamic Analyses

Pharmacokinetic

The primary PK parameters of lenvatinib in the combination will be calculated using noncompartmental analysis and compared with historical data after a 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 subject 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/PD 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 signs, and 12-lead ECG parameters. If needed, the changes from baseline will also be summarized.

Sample Size Rationale

A sample size of approximately 30 subjects (N=6 to 10 for DLT evaluation part and N=20 for Expansion part) will be enrolled in this study. This is not based on statistical power considerations. As of Amendment 03, Expansion part may be further expanded up to approximately 94 evaluable subjects. For this expansion decision, 2 interim analyses will take place when 20 (6 subjects for DLT evaluation part plus 14 subjects for Expansion part) and 56 subjects (6 subjects for DLT evaluation part plus 50 subjects for Expansion part) have sufficient follow-up to be evaluated for response. The decision to expand enrollment will be based on the results of 2 interim analyses, which will spend $\beta = 0.012$ and $\beta = 0.024$ at the first and second interim analyses, respectively. The decision to expand enrollment will be assessed by mRECIST based on investigator review.

Based on an assumption of H0: 25% ORR and H1: 45% ORR, the 100-subject design with two futility analyses has approximately 96% statistical power at 2-sided $\alpha = 0.02$ (that corresponds to 1-sided $\alpha = 0.01$). At the first interim analysis (N = 20), if there are more than 5 responses, then approximately 36 additional subjects will be enrolled. At the second interim analysis (N = 56), if there are more than 16 responses, approximately 44 additional subjects will be enrolled. If there are 5 or fewer responses at the first interim analysis (N=20) or 16 or fewer responses at the second interim analysis (N=56), the sponsor may decide whether to expand enrollment based on clinical outcome (eg, DOR).

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AASLD	American Association for the Study of Liver Diseases
ADA	anti-drug antibody
AE	adverse event
AFP	α-fetoprotein
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCLC	Barcelona Clinic Liver Cancer
β-hCG	beta-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BOR	best overall response
BP	blood pressure
BW	body weight
C#/D#	Cycle#/Day#
CA	competent authority
CBC	complete blood count
CBR	clinical benefit rate
cf-nucleic acid	cell free nucleic acid
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	clinical laboratory improvement amendments
C_{max}	maximum concentration
CP	Child-Pugh
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CRA	clinical research associate

Abbreviation	Term
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CV	curriculum vitae
CYP	cytochrome P450
Dbil	direct bilirubin
DCR	disease control rate
DKA	diabetic ketoacidosis
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
EDC	electronic data capture
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer
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
γ-GTP	gamma-glutamyltransferase
GI	gastrointestinal
hCG	human chorionic gonadotropin
HBcAb	hepatitis B core antibody
HBeAg	hepatitis B e antigen
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen

Abbreviation	Term
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV Ab	human immunodeficiency virus antibody
HNSCC	squamous cell carcinoma of head and neck
HRQoL	Health Related Quality of Life
HU	Hounsfield Units
HUVEC	human umbilical vein endothelial cell
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICL	imaging core laboratory
IEC	independent ethics committee
IIR	independent imaging review
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
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
LLT	lower level term
LMWH	low-molecular-weight heparin
LN	lymph node
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified RECIST
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

Abbreviation	Term
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	not evaluable
NN	Non-CR/Non-PD
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)
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PK/PD	pharmacokinetics/pharmacodynamic
PO	per os, orally
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PS	performance status
PT	preferred term
Q3W	every 3 weeks
QD	once daily
QOD	every other day
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RET	ret proto-oncogene
RNA	ribonucleic acid

Abbreviation	Term
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	Système International
SOC	system organ class
SOD	sum of diameter
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virological response
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TAM	tumor-associated macrophage
Tbil	total bilirubin
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TKI	tyrosine kinase inhibitor
t_{max}	time to maximum concentration
TNM	tumor-node-metastasis
TSH	thyroid stimulating hormone
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
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/Independent Ethics Committees

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

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

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

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. It is estimated that the study duration will be 36 months. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

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

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- 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
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

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

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

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

For 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 approximately 2 investigational sites in Japan for DLT evaluation part, and multiple centers in Japan, North America, and Europe in Expansion part.

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

7 INTRODUCTION

Study E7080-J081-116 is planned to evaluate the tolerability and safety of a combination of lenvatinib plus pembrolizumab in subjects with hepatocellular carcinoma (HCC). The primary objective is to confirm the tolerability and safety for the combination regimen. The tolerability and safety of lenvatinib 12 mg (Body Weight [BW] ≥60 kg) or 8 mg (BW <60 kg) once daily (QD) orally and pembrolizumab 200 mg every 3 weeks (Q3W) intravenous (IV) will be evaluated in this study. As secondary objectives, the pharmacokinetic (PK) profile and the efficacy of the regimen will be assessed. As of Amendment 03, ORR and DOR in Expansion part by mRECIST and RECIST 1.1 based on IIR analysis are added in primary objective.

7.1 Indication

7.1.1 Hepatocellular Carcinoma (HCC)

Liver cancer is the 6th most common cancer (782,000 new cases; 554,000 cases in men and 228,000 cases in women) and the 2nd cause of cancer related death (745,000 cases) which accounted for 9.1% of all cancers in 2012 (Ferlay, et al, 2015). HCC represents more than 90% of primary liver cancers and is a major global health problem. The majority of the HCC occur in Asia or Africa, however, the incidence has been rising in a number of low-rate areas including Europe and United States (EASL-EORTC Clinical Practice Guidelines, 2012).

HCC is associated with chronic liver disease, in particular cirrhosis. Major causes of cirrhosis include hepatitis B virus (HBV), hepatitis C virus (HCV), and alcoholic liver disease. Hepatitis B is the most frequent underlying cause of HCC, with an estimated 300 million persons with chronic infection worldwide. Chronic HBV carriers have a 5- to 15-fold increased risk of HCC compared with the general population (El-Serag and Rudolph, 2007). Chronic HCV infection is also a major risk factor for HCC. The risk of HCC was increased 17-fold in one study of HCV-infected patients compared with HCV-negative controls (Donato, et al., 2002).

The prognosis for advanced HCC is very poor. Although therapies including arterial infusion and radiation therapy have been tried, none has proven highly successful (Llovet, et al., 2003). Sorafenib is the current standard of therapy for advanced HCC patients following clinical results from the 2 pivotal trials in Western and Asian patients (Llovet, et al., 2008; Cheng, et al., 2009).

7.1.2 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 and Hicklin, 2008; Ferrara, et al., 2003; Hattori, et al., 2002; Laakkonen, et al., 2007; Tammela and Alitalo, 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, et al., 2005; Turner and Grose, 2010; Matsui, et al., 2004; Hirota, et al., 1998; Williams, 2002; Kondo, et al., 2006; Phay and Shah, 2010; Gild, et al., 2011; Hirota, et al., 2003; Oseini and Roberts, 2009) and anticancer treatment may be improved if their receptor tyrosine kinases (RTKs) are inhibited simultaneously.

Lenvatinib mesilate 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 preclinical 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 in vivo studies where human cancer cells were 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 to be well tolerated within the therapeutic range.

HCC stimulates the development of arterial vessels in the process of progression, and it also expresses high levels of VEGF (Yamaguchi, et al., 1998; Poon, et al., 2004). An angiogenesis inhibitor, therefore, which selectively inhibits VEGF receptors, could be a therapeutic agent that selectively treats HCC with little effect on background hepatic disease.

While lenvatinib is expected to induce tumor necrosis and suppression of progression by inhibiting angiogenesis and blocking blood flow in HCC with high expression of VEGF, an additional incremental benefit (compared with conventional anticancer agents) is that lenvatinib may have the potential for lower levels of toxicity in patients with HCC who have chronic hepatic disease. Because it selectively affects blood vessels, lenvatinib may also be less likely to induce resistance after long-term treatment since endothelial cells are unlikely to become resistant.

Lenvatinib is currently being evaluated in several clinical trials including patients with HCC, renal cell carcinoma, non-small cell lung cancer (NSCLC), endometrial cancer, glioma, melanoma, and ovarian cancer.

Use of lenvatinib 24 mg QD for the treatment of differentiated thyroid cancer has been approved by United States (US) FDA, European Union (EU) and Japan regulatory agencies. In addition, the once daily combination of 18 mg lenvatinib and 5 mg everolimus for patients with advanced renal cell carcinoma following 1 prior anti-angiogenic therapy was approved by the US FDA, and approved by EU for advanced renal cell carcinoma following one prior VEGF targeted therapy.

Concerning HCC, a Phase 1/2 study (E7080-J081-202) has been conducted, which showed clinical activity of lenvatinib monotherapy in patients with advanced HCC. Based on review of the safety and pharmacokinetic data derived from this Phase 1/2 study, lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) QD orally was established for Phase 3 study of lenvatinib monotherapy in patient with unresectable HCC (E7080-G000-304) (see Section 7.2.2.1 and 7.2.2.2).

7.1.3 PD-1 Inhibitors and Pembrolizumab

Antitumor immunity is often ineffective due to the tight regulation associated with the maintenance of immune homeostasis (Stagg and Allard, 2013). Recent studies have shown that cancer cells, as well as stromal cells and immune cells in the cancer microenvironment can upregulate expression of the B7 family of inhibitory molecules. These are peripheral membrane proteins found on activated antigen presenting cells (Coico, et al., 2003). Compelling evidence indicates that B7 proteins can suppress T-cell responses (Chen, 2004; Sharpe and Freeman, 2002) aiding tumor immune evasion. These negative signals are largely provided by 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, programmed cell death protein 1 ligand (PD-L1), has been shown to be associated with poor prognosis in melanoma and hepatocellular carcinoma (Gadiot, et al., 2011; Gao, et al., 2009; Topalian, 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 (HNSCC), and other tumors (Brahmer, et al., 2012; Hamid and Carvajal, 2013; Philips and Atkins, 2015; Robert, et al., 2014; Motzer, et al., 2015).

HCC is reported to be typically inflammation-associated and can be immunogenic (Hato, et al., 2014). Infection with HBV and HCV is associated with up-regulation of PD-1 (Xu, et al., 2014; Barathan, et al., 2015) and upregulation of circulating PD-L1/PD-1 is associated with poor prognosis in patients with HBV-related HCC (Zeng, et al., 2011). Concerning HCC, recently it was also reported that nivolumab (fully human IgG4 PD-1 antibody) showed anti-cancer effects in the interim data of phase 1/2 trial (El-Khoueiry, et al., 2015). Therefore, it is expected that PD-1 blockade with pembrolizumab, another anti-PD-1 antibody with similar efficacy and toxicity as nivolumab, may improve clinical outcomes in HCC patients as well.

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.

Concerning HCC, **studies of Phase 2 (MK-3475-224/KEYNOTE-224) and Phase 3 (MK-3475-240/KEYNOTE-240)** of pembrolizumab 200 mg Q3W for previously systemically treated advanced HCC are on-going. (Clinicaltrials.gov; KEYNOTE-224, KEYNOTE-240)

7.2 Combination of Lenvatinib Plus Pembrolizumab

7.2.1 Nonclinical

It is reported that VEGF/VEGFR signaling exhibits proangiogenic properties but also may contribute to an immunosuppressive microenvironment (Gabrilovich, et al., 1996; Huang, et al., 2007; Terme, et al., 2013; Voron, et al, 2015). Therefore, it is expected that lenvatinib which inhibits VEGFR, may 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 was more effective than 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 and Matsui, 2015). Because TAM cells produced interleukin 10 (IL-10) and transforming growth factor, beta 1 (TGFβ) (Noy and Pollard, 2014), lenvatinib

might increase antitumor immunity in the CT26 model and up-regulate the effects of the PD-1 signal inhibitors.

Antitumor activity of combination treatment of lenvatinib with anti-PD-1 mAb was also examined in H22 murine hepatocellular carcinoma cell syngeneic model. The result showed that combination treatment with lenvatinib and PD-1 mAb was more effective than single-agent treatment in this model (Kato, et al., 2016).

Thus, in addition to the direct anti-angiogenic effects of lenvatinib, the immune-modulating effect of lenvatinib may also result in potent combination effect with PD-1 signal inhibitors in multiple syngeneic tumor models.

7.2.2 Clinical Studies

7.2.2.1 E7080-J081-202 (Phase 1/2 of Lenvatinib Monotherapy for HCC)

A Phase 1/2 clinical study (E7080-J081-202) has been conducted in subjects with advanced HCC for which effective therapeutic methods have not been established. This was a multicenter, open-label study of lenvatinib (8 to 16 mg QD for 4 weeks per cycle) consisting of a Dose Escalation Component (Phase 1 part) and an Expansion Component (Phase 2 part) in subjects with advanced HCC in Asia (Japan and Korea). Based on the results of Phase 1, the recommended dose for Phase 2 was determined to be 12 mg for HCC subjects with Child-Pugh A (CP-A, score 5–6). A total of 46 subjects were enrolled in Phase 2 part.

In the Phase 2 part, efficacy assessment based on the independent imaging review (N=46) indicated that 17 (37.0%) subjects had PR by mRECIST for HCC. Nineteen (41.3%) subjects had SD (ie, lasting ≥7 weeks) with durable SD (ie, lasting ≥16 weeks) reported in 15 (32.6%) subjects. Based on the independent imaging review, the median time to progression (TTP) was 7.4 months. An overall survival (OS) analysis with a minimum follow-up period of 12 months indicated a median OS of 18.7 months.

All the 46 subjects enrolled in Phase 2 part experienced at least 1 treatment-emergent adverse event (TEAE), and 44 subjects experienced treatment-related TEAEs. Twenty-two of 46 subjects reported a serious TEAE, and in 14 subjects the serious TEAEs were considered treatment-related. Grade 3 or above TEAEs were reported for 45 subjects and were considered treatment-related in 40 subjects. Sixteen subjects experienced AEs that led to discontinuation of study treatment, and 10 AEs were considered to be related to treatment medication. Thirty-two subjects experienced treatment-related TEAEs that resulted in dose reduction and 20 subjects had treatment-related TEAEs that led to interruption of study drug administration.

Overall, the most common TEAEs (occurring in ≥30% of subjects overall) were hypertension (76.1%; 35/46 subjects), palmar-plantar erythrodysaesthesia syndrome (65.2%; 30/46 subjects), decreased appetite, proteinuria (each in 60.9%; 28/46 subjects), fatigue (54.3%; 25/46 subjects), diarrhoea (43.5%; 20/46 subjects), constipation (41.3%; 19/46 subjects),

nausea, dysphonia (each in 37.0%; 17/46 subjects), thrombocytopenia, oedema peripheral (each in 34.8%; 16/46 subjects), and weight decreased (30.4%; 14/46 subjects). The most frequently occurring Grade 3 or above TEAEs were hypertension (54.3%; 25/46 subjects), thrombocytopenia (21.7%; 10/46 subjects), proteinuria (19.6%; 9/46 subjects), platelet count decreased, hepatic encephalopathy, diarrhoea (each in 13.0%; 6/46 subjects), and palmar-plantar erythrodysaesthesia syndrome (8.7%; 4/46 subjects). Thrombocytopenia and cardiac tamponade were reported at Grade 4 (each in 2.2%; 1/46 subject).

Although most AEs were controllable by dose interruption and dose reduction, 20 subjects had dose reduction within the first treatment cycle, and 17 of these subjects weighed less than 60 kg. Subsequent analysis of the study results indicated a relationship between area under the concentration × time curve (AUC)/body weight (BW) and dose reduction/discontinuation within the first treatment cycle. In order to reduce the number of dose reductions and withdrawals due to AEs within the first treatment cycle, a weight-based dosing schedule has been established with 2 categories. The starting lenvatinib dose will be 12 mg administered orally QD in HCC subjects who weigh 60 kg or more, and the lenvatinib dose will be 8 mg administered orally QD in subjects who weigh less than 60 kg.

Based on the above analysis from the Phase 1/2 study, lenvatinib is expected to be a promising treatment for advanced HCC patients.

7.2.2.2 E7080-G000-304 (Phase 3 of Lenvatinib Monotherapy for HCC)

E7080-G000-304 is a multicenter, randomized, open-label, Phase 3 trial designed to compare the safety and efficacy of lenvatinib versus sorafenib in subjects with Child-Pugh A, unresectable HCC. The purpose of this study is to compare the OS of subjects with unresectable HCC treated with lenvatinib versus sorafenib. Subjects were randomized 1:1 to receive either of the following treatment groups: "Lenvatinib group: 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) QD" and "Sorafenib group: 400 mg twice daily (BID)". This study was completed on 13 November 2016 (data cutoff for the primary analysis). According to the results of the study, lenvatinib met the statistical criteria for non-inferiority of OS compared to sorafenib, and showed statistically significant and clinically meaningful improvement for PFS, TTP and ORR.

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

E7080-A001-111 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, HNSCC or melanoma [excluding uveal melanoma]), which is being conducted in the 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 was reduced, if necessary, to either 20 mg or 14 mg. In the lenvatinib 24 mg cohort, 2 dose-limiting toxicities (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 QD lenvatinib and 10 additional subjects (total of 6 renal cell carcinoma, 1 NSCLC, 1 Melanoma and 2 Endometrial) started treatment. There were no DLTs in the 2nd cohort and the MTD and RP2D were determined at 20 mg lenvatinib QD in combination with 200 mg Q3W of pembrolizumab.

In Phase 2, subjects are assigned by tumor type to up to 6 cohorts (10 or 20 evaluable subjects per cohort) to receive the MTD to assess the safety and efficacy of the combination in the selected tumor-types. This phase is ongoing.

7.2.2.4 E7080-J081-115 (Phase 1b of Lenvatinib Plus Pembrolizumab for Selected Solid Tumors in Japan)

Study E7080-J081-115 is being conducted for subjects with selected solid tumors in Japan. Basically the design of this study will be the mirror of the Phase 1b part of E7080-A001-111 conducted in US. The tolerability and safety of lenvatinib 20 mg QD and pembrolizumab 200 mg Q3W IV, which was determined as MTD and RP2D in Study 111, will be confirmed in Japanese subjects in this Study 115. The primary objective is to confirm the tolerability and safety for combination regimen of lenvatinib plus pembrolizumab in subjects with selected solid tumors.

7.3 Study Rationale

This multicenter, open-label Phase 1b study will evaluate the tolerability and safety of lenvatinib in combination with pembrolizumab in subjects with advanced/unresectable HCC. This study will begin with lenvatinib 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) QD and pembrolizumab 200 mg Q3W in subjects with HCC on a 21-day treatment cycle. For the confirmation of the tolerability of the dose level, DLTs will be evaluated during the first cycle (21 days). Treatment will continue until disease progression, development of unacceptable toxicity, withdrawal of consent, or discontinuation of this study by the sponsor.

HCC stimulates development of arterial vessels in the process of progression and it shows high expression of VEGF (Yamaguchi, et al., 1998; Poon, et al., 2004). Lenvatinib, an angiogenesis inhibitor which selectively inhibits VEGF receptors, could be a therapeutic agent that treats HCC with little effect on background hepatic disease.

Likewise, HCC is reported to be typically inflammation-associated and can be immunogenic (Hato, et al., 2014). Infection with HBV and HCV is associated with up-regulation of PD-1 (Xu, et al., 2014; Barathan, et al., 2015) and upregulation of circulating PD-L1/PD-1 is associated with poor prognosis in patients with HBV-related HCC (Zeng, et al., 2011). Clinically, it has been reported that an anti-PD-1 antibody showed anti-cancer effects (El-Khoueiry, et al., 2015). Therefore, it is expected that PD-1 blockade with pembrolizumab may improve clinical outcomes in HCC patients.

In preclinical studies, the effect of combining lenvatinib with PD-1/L1 mAbs has been investigated utilizing multiple kinds of cancer cells including an H22 murine hepatocellular carcinoma cell syngeneic model. In the model, the combination treatment with lenvatinib and PD-1 mAb showed superior antitumor effects compared with either compound alone. Lenvatinib significantly decreased the TAM population and it was suggested that lenvatinib might increase antitumor immunity in the CT26 model and up-regulate the effect of the PD-1 signal inhibitors (Kato and Matsui, 2015).

Therefore, the combination therapy of lenvatinib plus pembrolizumab might become a potential treatment for HCC.

The starting dose of lenvatinib for the combination trial will be 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg). These doses are based on the review of the safety and pharmacokinetic data derived from the Phase 1/2 study of lenvatinib in subjects with HCC (E7080-J081-202), which is adopted in the ongoing Phase 3 study of lenvatinib monotherapy in subjects with unresectable HCC (E7080-G000-304). While the recommended dose for the Phase 2 part was determined to be 12 mg for HCC subjects with CP-A based on the results of Phase 1 part, in order to reduce the number of dose reductions and withdrawals due to AEs within the first treatment cycle, a weight-based dosing schedule has been established with the 2 categories of 12 mg QD (BW ≥60 kg) and 8 mg QD (BW <60 kg) (see Section 7.2.2.1).

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 other 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 BW 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.

While the pembrolizumab 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as above, safety of single agent pembrolizumab in subjects with HCC is being investigated. The studies of Phase 2 (MK-3475-224/KEYNOTE-224) and Phase 3 (MK-3475-240/KEYNOTE-240) for previously systemically treated advanced HCC are ongoing (Clinicaltraials.gov; KEYNOTE-224, KEYNOTE-240).

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.

8 STUDY OBJECTIVES

8.1 Primary Objectives

- To evaluate the tolerability and safety for combination of lenvatinib plus pembrolizumab in subjects with hepatocellular carcinoma (HCC)
- (Expansion part) To evaluate objective response rate (ORR) and duration of response (DOR) by modified Response Evaluation Criteria in Solid Tumors for HCC (mRECIST) and RECIST 1.1 based on independent review (IIR)

8.2 Secondary Objectives

- (DLT evaluation Part) To evaluate ORR and DOR by mRECIST (based on investigator review and IIR), and by RECIST1.1 based on IIR
- (Expansion Part) To evaluate ORR and DOR by mRECIST based on investigator review
- To evaluate the following efficacy endpoints by mRECIST (based on investigator review and IIR) and RECIST1.1 (based on IIR) :
  - Progression-free survival (PFS)
  - Time to progression (TTP)
  - Time to response (TTR)
- Overall survival (OS)
- 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 mRECIST (based on investigator review and IIR) and RECIST1.1 (based on IIR):
  - Disease control rate (DCR)
  - Clinical benefit rate (CBR)
- To evaluate the impact of treatment on Health Related Quality of Life (HRQoL) for subjects treated using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, HCC-specific EORTC QLQ-HCC18 questionnaire and European Quality of Life questionnaire.

  For the subjects in Expansion part added as of the protocol Amendment 03, HRQoL will be evaluated using the EORTC QLQ-C30 and the HCC specific supplement QLQ-HCC18. HRQoL will also be evaluated using the generic EuroQuol five dimension five level (EQ-5D-5L) questionnaire.
- 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 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

This is an open-label Phase 1b study. This study will evaluate the tolerability and safety of lenvatinib in combination with pembrolizumab in subjects with HCC.

This study will begin with lenvatinib 12 mg (Body Weight [BW] ≥60 kg) or 8 mg (BW <60 kg) /day orally and pembrolizumab 200 mg (every 3 weeks [Q3W], intravenous [IV]) in subjects with HCC. Tolerability of this dose level will be evaluated by dose-limiting toxicities (DLTs) during the first cycle (21-day treatment cycle).

In this dose level, 3 subjects will be enrolled first. If 0 or 1 of 3 subjects in a given dose level cohort experiences a DLT, then 3 more subjects will be enrolled into that dose level. If 0 or 1 of 6 subjects in a given dose level cohort experiences a DLT, the dose level will be considered tolerable (Figure 1). Additional 4 subjects can be enrolled without DLT evaluation if further safety information is considered necessary based on the discussions between the sponsor and investigators.

Enrollment will be interrupted if 2 or more DLTs are observed in this 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, after sponsor and investigators' review regarding the nature and severity of the DLTs, an additional 4 subjects (10 subjects in total for DLT evaluation) will be enrolled, and that dose level will be considered to be tolerable if DLT is observed in 3 or less of the 10 subjects in total (Figure 1). An independent medical advisor as third party may be consulted for the review as needed.

In this dose level, at least 3 subjects treated with lenvatinib 12 mg once daily (QD) and pembrolizumab 200 mg Q3W IV (BW ≥60 kg) need to be included in the 6 subjects for DLT evaluation. (In case of the 10 subjects for DLT evaluation, at least 5 subjects (BW ≥60 kg) treated with lenvatinib 12 mg QD and pembrolizumab 200 mg Q3W IV need to be included.)

Cohort of reduction to lower dose level (lenvatinib) or study discontinuation will be considered, if this dose level (12 mg [BW ≥60 kg] or 8 mg [BW <60 kg] lenvatinib plus 200 mg pembrolizumab) is not tolerable, upon discussions between the sponsor and investigators, and the protocol will be amended as necessary (Figure 1). An independent medical advisor as third party maybe 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.

For determination of the recommended phase 2 dose, all episodes of Grade 3 or 4 thrombocytopenia and neutropenia beyond Cycle 1 will be taken into consideration.

If the dose level is confirmed to be tolerable, an additional (approximately) 20 subjects will be enrolled for consolidation of PK data and safety and efficacy as the **Expansion part**. As of Amendment 03, the Expansion part may be further expanded up to approximately 94 subjects. The decision to expand enrollment will be based on the results of 2 interim analyses that will take place when 20 (6 subjects for DLT evaluation part plus 14 subjects for Expansion part) and 56 subjects (6 subjects for DLT evaluation part plus 50 subjects for Expansion part) have sufficient follow-up to be evaluated for response. The decision to expand enrollment will be assessed by mRECIST based on investigator review. At the first interim analysis (N = 20), if there are more than 5 responses, then approximately 36 additional subjects will be enrolled. At the second interim analysis (N = 56), if there are more than 16 responses, approximately 44 additional subjects will be enrolled. If there are 5 or fewer responses at the first interim analysis (N = 20) or 16 or fewer responses at the second interim analysis (N=56), the sponsor may decide whether to expand enrollment based on other clinical outcome (eg, DOR). At least 5 subjects (BW ≥60 kg) treated with Lenvatinib 12 mg QD and at least 5 subjects (BW <60 kg) treated with Lenvatinib 8 mg QD will be included in Expansion part.

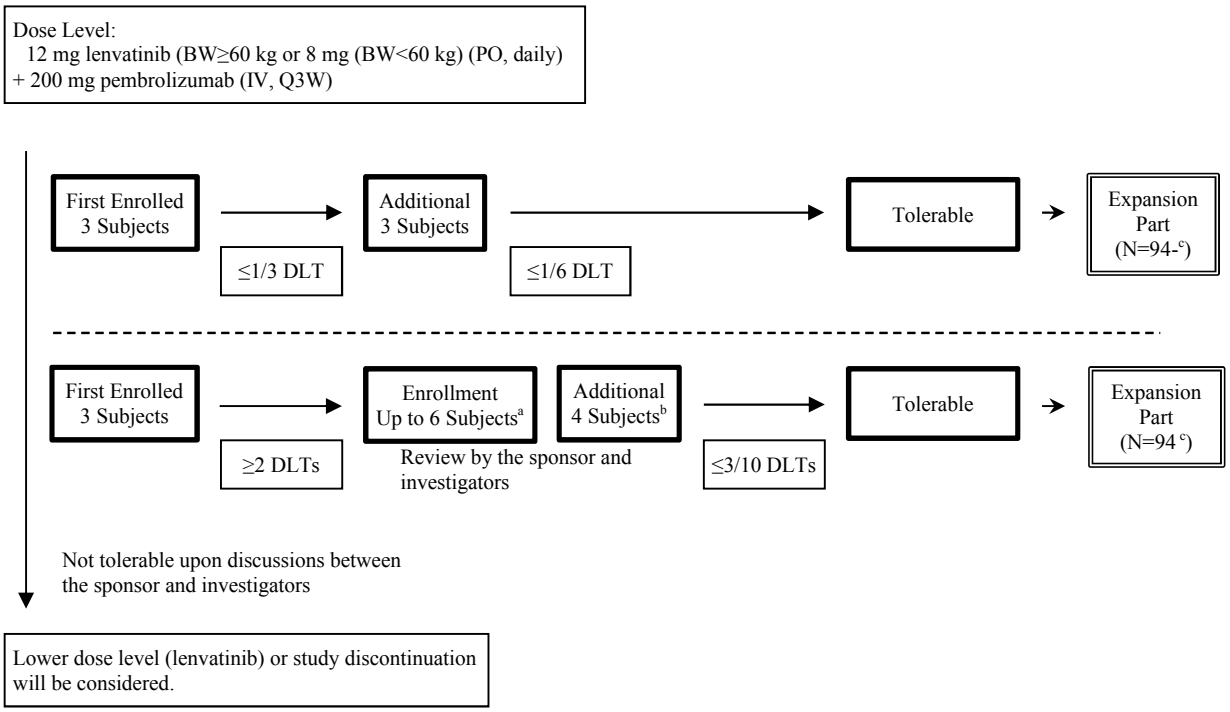


Figure 1 Confirmation of the Tolerability

DLT = dose-limiting toxicity, IV = intravenous, PO = per os (orally), Q3W = every 3 weeks.
a: After sponsor and investigators' review, enrollment may continue for up to 6 subjects based on the nature and severity of the DLTs.
b: After sponsor and investigators' review regarding the nature and severity of the DLTs, an additional 4 subjects (10 subjects in total for DLT evaluation) will be enrolled.
c: Expansion part may be expanded to enroll up to approximately 94 evaluable subjects.

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 week 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 above febrile neutropenia[a] • Grade 4 thrombocytopenia lasting ≥7 days or Grade 3 thrombocytopenia associated with clinically significant hemorrhage or bleeding and/or requiring platelet transfusion

Nonhematologic toxicity	• Grade 4 or 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 gastrointestinal perforation
	• Grade 3 wound dehiscence requiring medical or surgical intervention
	• Grade 3 thromboembolic event

	Any Grade 3 nonhematologic laboratory value (except AST/ALT) if: • Medical intervention is required to treat the subject, or the abnormality leads to hospitalization Note: Abnormal laboratory values to which treatment and hospitalization is not required can be deemed a non-DLT
	• AST/ALT >10.0×ULN, which does not resolve within 1 week, or else is clinically symptomatic.

ANC = absolute neutrophil count, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events v4.03, DLT = dose-limiting toxicity, ULN = upper limit of normal.
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.

Adverse events (AEs) with a clear alternative explanation (eg, due to disease progression) 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).

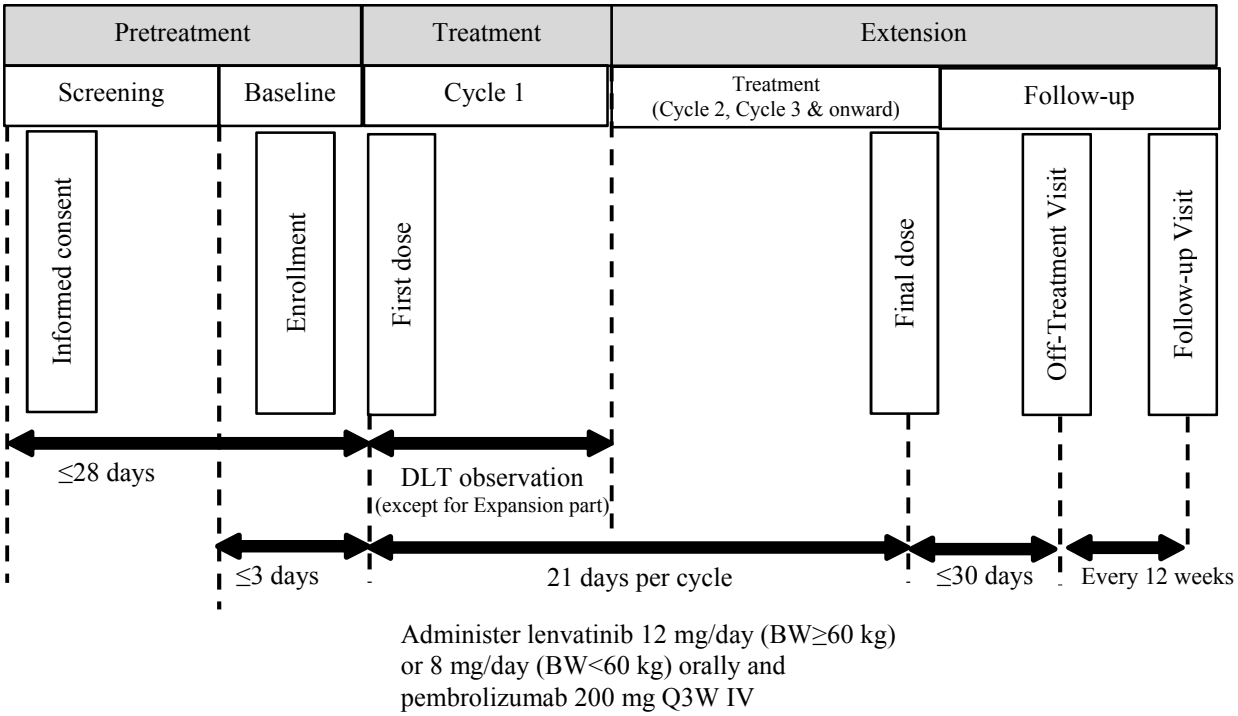


Figure 2 Study Design
BW = body weight, DLT = dose-limiting toxicity, IV = intravenous, Q3W = every 3 weeks.

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 except for the Expansion part; 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 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. Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor termination of the study. 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 and the Follow-up.

- The Off-Tx Visit will occur within 30 days following the last dose of study treatment. Following the completion of the Off-Tx Visit, subjects will transition to the Follow-up.
- The Follow-up will continue as long as the study subject is alive unless the subject withdraws consent or until the sponsor terminates the study. In the Follow-up, subjects will be treated by the investigator according to the prevailing local standard of care. For survival and subsequent anticancer treatments, subjects will be followed every 12 weeks (±1 week) or at sponsor's request. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email. The survival follow-up will be continued for up

to 2 years after Cycle1/Day1 (C1D1) of the last subject enrolled in the Expansion part. The sponsor may decide to terminate survival follow-up anytime during the Extension Phase or when all subjects have discontinued study treatment.

As required by some regulatory agencies, the following estimates are provided:

- The study began in February 2017 and will end on or before February 2020.
- The maximum estimated period for the study is anticipated to be approximately 36 months. However, subjects will continue to receive study treatment as long as they demonstrate clinical benefit. Refer to Section 9.3.3.1 Discontinuation Criteria by Subject for details.

9.1.4 Second Course Phase (Pembrolizumab Retreatment Period)

All subjects who stop treatment with lenvatinib plus pembrolizumab and have SD or better may be eligible to receive up to 1 additional year of treatment with pembrolizumab (17 cycles), with or without lenvatinib, if they develop PD after stopping study treatment during the initial treatment period. This retreatment period is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions.

Either:

- Stopped initial treatment with lenvatinib plus pembrolizumab after attaining an investigator-determined confirmed CR according to mRECIST
  - Was treated for at least 8 cycles with lenvatinib plus pembrolizumab before discontinuing therapy
  - Received at least 2 treatment cycles of lenvatinib plus pembrolizumab beyond the date when the initial CR was declared

Or:

- Had SD, PR, or CR and stopped lenvatinib plus pembrolizumab treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

***All of the following*:**

- Develops investigator-determined radiographic disease progression, per mRECIST after stopping initial treatment with pembrolizumab
- No new anticancer treatment was administered after the last dose of study treatment

- The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria
- The study is ongoing

The investigator should perform tumor assessments for all subjects who are retreated according to the local standard of care, but not less frequently than every 12 weeks (see Section 9.5.1.3.1 for details). During the Second Course (Pembrolizumab Retreatment) Phase, scans will no longer be sent to the imaging core lab. If the subject has an objective response or disease progression during retreatment, it will not be counted as an event for the primary analysis of PFS or ORR in this study.

Visit requirements for the Second Course Phase are outlined in Table 10 in Section 9.5.2.1.

9.2 Discussion of Study Design

This open-label Phase 1b study was designed to evaluate the tolerability and safety of lenvatinib in combination with pembrolizumab in subjects with HCC. 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. Subjects with HCC to be studied in this study 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

Approximately 30 subjects will be enrolled in Japan and US (N=6 to10 for DLT evaluation part and N=20 for Expansion part). As of Amendment 03 the enrollment for Expansion part may be further expanded up to approximately 94 evaluable subjects. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

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

1. Subjects must have confirmed diagnosis of HCC with any of the following criteria:
   - Histologically or cytologically confirmed diagnosis of HCC, excluding fibrolamellar, sarcomatoid or mixed cholangio-HCC tumors
   - Clinically confirmed diagnosis of HCC according to American Association for the Study of Liver Diseases (AASLD) criteria, including cirrhosis of any etiology and/or chronic hepatitis B or C infection
2. HCC for which no other appropriate therapy is available

Note: Subjects basically should receive prior standard therapy including sorafenib. However, if the investigator judges the therapy is not appropriate for the subject, the prior standard therapy is not necessarily mandated for the eligibility.

Expansion Part: No prior systemic therapy for advanced/unresectable HCC

Note: Subjects who have received local hepatic injection chemotherapy are eligible.

3. Subjects categorized to stage B (not applicable for transarterial chemoembolization [TACE]), or stage C based on Barcelona Clinic Liver Cancer (BCLC) staging system
4. At least 1 measurable target lesion according to mRECIST meeting the following criteria.
   - Hepatic lesion
     i. The lesion can be accurately measured in at least 1 dimension as ≥1.0 cm (viable tumor for typical; and longest diameter for atypical), and
     ii. The lesion is suitable for repeat measurement
   - Nonhepatic lesion
     i. Lymph node (LN) lesion that measures at least 1 dimension ≥1.5 cm in the short axis, except for porta hepatis LN that measures ≥2.0 cm in the short axis
     ii. Non-nodal lesion that measures ≥1.0 cm in the longest diameter

   Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression to be deemed a target lesion. Subjects whose only target lesion(s) is in bone will be excluded.
5. Child-Pugh score A
6. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1
7. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week prior to the C1D1
8. 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
9. Adequate bone marrow function:
   - Absolute neutrophil count (ANC) ≥1500/mm^3 (≥$1.5\times10^3/\mu L$)
   - Platelets ≥75,000/mm^3 (≥$75\times10^9/L$)
   - Hemoglobin ≥8.5 g/dL
10. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤2.3
11. Adequate liver function, defined as:
    - Bilirubin ≤2.0 mg/dL
    - Aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alanine aminotransferase (ALT) ≤5×ULN

12. Total triiodothyronine (T3) or free T3 and free thyroxine (T4) are within normal limits (control by thyroid replacement therapy is acceptable). As of Amendment 03, subjects with T3, free T3, or free T4 abnormalities at screening who are asymptomatic can be eligible.
13. Males or females age ≥18 years at the time of informed consent
14. Life expectancy of 12 weeks or more
15. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol
16. **Expansion Part**: Archival tumor tissue or a newly obtained biopsy must be available prior to the first dose of study drug for biomarker analysis.
    - Patients without archival tumor tissue and with inaccessible tumors for biopsy specimens can be enrolled without a biopsy.
    - 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.

    Note: Collection of archival tumor tissue or a newly obtained biopsy prior to the first dose of study treatment will be optional in the patients who are not enrolled in Expansion cohort

9.3.2 Exclusion Criteria

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

1. Imaging findings for HCC corresponding to any of the following:
    - HCC with ≥50% liver occupation
    - Clear invasion into the bile duct
    - Portal vein invasion with Vp4
2. Prior anticancer treatment within 28 days (or within 14 days in case of sorafenib) 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 and controlled stable cases).
   Note: Refer to inclusion criteria regarding hypertension.
3. Any blood enhancing treatment (including blood transfusion, blood products, or agents that stimulate blood cell production, eg, granulocyte colony-stimulating factor [G-CSF]) within 28 days prior to the first dose of study drugs.
4. Prior treatment with lenvatinib or any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
5. Subjects must have recovered adequately from any complications from major surgery prior to starting therapy.
6. 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.

7. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.
8. 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.
9. Prolongation of QTc (Fridericia formula) interval to >480 ms.
10. Gastrointestinal bleeding event or active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study drug.
11. Bleeding or thrombotic disorders or use of factor X inhibitors or anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin is permitted. Antiplatelet agents are prohibited throughout the study.
12. Gastric or esophageal varices that require interventional treatment within 28 days prior to first dose of study drug are excluded. Prophylaxis with pharmacologic therapy (eg, nonselective beta-blocker) is permitted.
13. Surgical arterial-portal venous shunt or arterial-venous shunt.
14. Active malignancy (except for HCC or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 36 months.
15. Active infection (any infection requiring systemic treatment). Hepatitis B or C [HBV/HCV] is allowed.
16. In case of HBsAg (+) subjects: Antiviral therapy for HBV must be given for at least 3 months prior to first dose of study drug, and HBV viral load must be less than 100 IU/mL prior to first dose of study drug.
    - Subjects who are HBsAg (+) and on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment.
    - Subjects without HBV prophylaxis who are anti-HBcAb (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA do not require prophylaxis.
    - Subjects with HBV prophylaxis who are anti-HBcAb (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA should continue the prophylaxis.
    - In all the subjects above, they need monitoring with HBV DNA every 3 weeks during the study treatment.
17. Therapy for HCV must be completed at least 4 weeks prior to first dose of study drug in case of Hepatitis C subjects who are on active HCV treatment. Hepatitis C subjects who are untreated or uncured may also be enrolled.
18. Has dual active HBV infection (HBsAg (+) and /or detectable HBV DNA) and HCV infection (anti-HCV Ab(+) and detectable HCV RNA) at study entry.
19. Meningeal carcinomatosis.
20. Subjects with CNS metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have

discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.

21. Subject is known to be positive for Human Immunodeficiency Virus (HIV).
22. History of clinically significant hepatic encephalopathy.
23. Serious nonhealing wound, ulcer, or bone fracture.
24. History of solid organ or hematologic transplant.
25. Any subject who cannot be evaluated by either triphasic liver computed tomography (CT) or triphasic liver magnetic resonance imaging (MRI) because of allergy or other contraindication to both CT and MRI contrast agents.
26. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial.
27. 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 10 mg/d of prednisone or equivalent) may be approved after consultation with the sponsor. The use of steroids in prophylaxis of allergic reaction by CT contrast agents will be allowed.
28. 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.
29. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis, or has a history of interstitial lung disease.
30. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
31. Has severe hypersensitivity (≥ Grade 3) to pembrolizumab or lenvatinib and/or any of their excipients.
32. Any subjects with non-GI fistula.

33. Subjects who meet any of the following criteria will be excluded from this study:
    1) 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.
    2) 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 [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing].

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

34. 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 #32) 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, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. The 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 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).

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis. The survival follow-up will be continued for up to 2 years after C1D1 of the last subject enrolled in the Expansion part.

9.3.3.1 Discontinuation Criteria by Subject

If a subject meets any of the following criteria, the investigator 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 mRECIST.) If progressive disease (PD) 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 determined 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 enrollment.

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 for up to 2 years after C1D1 at the longest. Subjects who stop study treatment after receiving 35 administrations of pembrolizumab for reasons other than progressive disease (PD) or intolerability, or subjects who attain a complete response (CR) and stop study treatment, may be eligible to receive a second course of treatment of up to 17 additional administrations of pembrolizumab (approximately 1 year).

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 in the subjects of DLT evaluation part) 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 in the subjects of DLT evaluation part.

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

9.4.1.3.1 CYCLE 1 (EXCEPT FOR EXPANSION PART)

Dose Modification in the Event of DLT

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

Dose Modification 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 (AND APPLIES TO CYCLE 1 AND ONWARD OF EXPANSION PART)

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.

Starting dose of lenvatinib will be based on baseline BW as follows:

- BW ≥60 kg — 12 mg QD. Study subjects will be orally administered lenvatinib as three 4-mg capsules
- BW <60 kg — 8 mg QD. Study subjects will be orally administered lenvatinib as two 4-mg capsules

Dose adjustments for management of intolerable toxicities will be made according to the guidelines provided in the table below.

Table 2 Lenvatinib Dose Reduction and Interruption Instructions

Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QOD]). Any dose reduction below 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.		
Nonhematologic Toxicities		
Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment[c]	No change
Intolerable Grade 2[c] and Grade 3[d,e,h]		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 more dose level
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4[g,h]: Discontinue Lenvatinib		
Hematologic Toxicities and Proteinuria		
Treatment-Related Toxicity[a]	**Management**	**Dose Adjustment**
Grade 1 or Grade 2[e]		
	Continue treatment[c]	No change
Grade 3[e]		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	No change
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 dose level
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fifth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discuss with sponsor
Grade 4[i]		
First occurrence	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 dose level
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Third occurrence[f] (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-2 or baseline	Discuss with sponsor

Note: Grading according to CTCAE v4.03.
AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, γ-GTP = γ-glutamyltransferase, CTCAE v4.03 = Common Terminology Criteria for Adverse Events Version 4.03, Na =

Table 2 Lenvatinib Dose Reduction and Interruption Instructions

sodium, ULN = upper limit of normal, QD = once daily.

a: An interruption of lenvatinib for more than 21 days (due to lenvatinib treatment-related toxicities) will require sponsor's approval before treatment can be resumed. During treatment interruption, repeat AEs assessment at least every 7 days (until restarting administration).

b: Excluding alopecia. Initiate optimal medical management for nausea, vomiting, diarrhea, and/or hypothyroidism prior to any lenvatinib treatment, interruption, or dose reduction. For treatment-related hypertension, refer to Management of Hypertension (Section 9.4.1.4.1) for dose modification guidelines.

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

d: Obese subjects with weight loss do not need to return to baseline or Grade 1 weight loss to restart lenvatinib. There should be no weight loss for at least 1 week, and subjects should be started at the lower dose and normal BMI should be used for future dose reductions.

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

f: Not applicable for subjects who start at 8 mg QD.

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

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

i: Only applicable to Hematologic Toxicities.

Table 3 Dose Reduction for Lenvatinib Treatment-Related Toxicity

Initial Lenvatinib Dose (mg, QD)	Adjusted Dose To Be Administered (mg, QD)		
	Reduction 1	Reduction 2	Reduction 3
12	8	4	4[a]
8	4	4[a]	

QD = once daily.

a: 4 mg every other day [QOD]. Any dose reduction below 4 mg every other day must be discussed with the sponsor.

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.

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

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 regarding non-hepatic drug-related

AEs or the following guidance for hepatic events of clinical interest. See Section 9.4.1.5 for supportive care guidelines, including use of corticosteroids, and **Guidance for Management of Hepatic Events of Clinical Interest** of Section 9.4.1.3.2 for dose modification and management of hepatic events of clinical interest.

Table 4 Dose Interval Modification Guidelines for Non-Hepatic Drug-Related Adverse Events Associated With Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3	Permanently discontinue at the first recurrence of Grade 3 colitis		
	Grade 4	Permanently discontinue		

Table 4 Dose Interval Modification Guidelines for Non-Hepatic Drug-Related Adverse Events Associated With Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement	• Monitor for signs and symptoms of thyroid

Table 4 Dose Interval Modification Guidelines for Non-Hepatic Drug-Related Adverse Events Associated With Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
			hormones (eg, levothyroxine or liothyroinine) per standard of care	disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not		

Table 4 Dose Interval Modification Guidelines for Non-Hepatic Drug-Related Adverse Events Associated With Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
		limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

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

See Table 5 for Infusion Reaction Treatment Guidelines in Section 9.4.1.5 for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Dosing interruptions are permitted in the case of medical/surgical events or for 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.

Guidance for Management of Hepatic Events of Clinical Interest:

Hepatic events of clinical interest will include any of the following events. All of these events will require holding pembrolizumab treatment. All cases of retreatment and permanent discontinuation must be reported to the sponsor. Refer to Sections 9.5.1.5.2 and 9.5.4.3.2 for further details.

a. ALT:
   i. Among subjects with baseline ALT <2×ULN: ALT ≥5×ULN
   ii. Among subjects with baseline ALT ≥2×ULN: ALT >3× the baseline level
   iii. ALT >500 U/L regardless of baseline level

b. AST:
   i. Among subjects with baseline AST <2×ULN: AST ≥5×ULN
   ii. Among subjects with baseline AST ≥2×ULN: AST >3× the baseline level
   iii. AST >500 U/L regardless of baseline level

c. Total Bilirubin:
   i. Among subjects with baseline levels <1.5 mg/dL: a value of >2.0 mg/dL
   ii. Among subjects with baseline levels that are ≥1.5 mg/dL: a value ≥2× the Baseline level
   iii. Total bilirubin >3.0 mg/dL regardless of baseline level

d. Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
   i. New onset ascites uncontrollable with diuretic
   ii. Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)
   iii. Hepatic Encephalopathy

Immediate Assessment

<u>All subjects</u>

- All subjects should be evaluated according to directions below within 72 hours of alert for non-overdose events of clinical interest
- Procedures:
  - Consider a consultation with a hepatologist

- Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B,C, D, E, Epstein-Barr virus, and cytomegalovirus
- Assess for ingestion of drugs/supplements with hepatotoxic potential
- Assess for alcohol ingestion
- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Repeat ALT, AST, Tbil, Dbil, ALP, γ-glutamyl transpeptidase, INR, and CBC with differential
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated by hepatologist

Hepatitis C-infected Subjects (including subjects who previously achieved SVR 12)

- In addition to the above, measure HCV RNA viral load

Hepatitis B-infected Subjects

- HBV DNA, HBsAg, HBeAg, anti-HBc (total and IgM), anti-HBe antibody, and anti-HBs antibody
- Subjects should be questioned about compliance with the use of anti-viral agents.

Permanent Discontinuation Criteria for Subjects With Non-Overdose Hepatic Events of Clinical Interest:

Pembrolizumab should also be permanently discontinued for:

- ALT >20×ULN
- Child-Pugh (CP) score of ≥9 points
- Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)[a]
- Hepatic Encephalopathy[a]
- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related.

a: Pembrolizumab is not necessarily discontinued if it is judged by Investigator that the AE is not associated with pembrolizumab (eg, lenvatinib treatment-related toxicity) after discussion with sponsor

Other subjects may be eligible for treatment interruption (and potential re-start) of pembrolizumab after discussion with the sponsor.

Diagnosis and Management of Non-Overdose Hepatic Events of Clinical Interests:

HCC subjects are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC subjects.

Hepatitis B Flare

Hepatitis B flares are characterized by rapid elevations of ALT and AST to >5×ULN and/or >3× baseline. ALT elevation to ≥10×ULN is common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (ie, limited/no elevations of bilirubin/ALP). Subjects who are compliant with anti-viral therapy should have continued suppression of HBV DNA at the time of flare; thus, detection of HBV DNA should prompt questioning of subjects for compliance. Laboratory abnormalities secondary to flare are typically observed for 3-5 weeks.

Among subjects with HBV, a flare should be considered if this pattern is observed and there is no evidence of an alternative etiology. Guidelines for subjects with a diagnosis of HBV flare are as follows:

- Care should be instituted in consultation with a hepatologist.
- For subjects who have detectable HBV DNA, re-institute anti-viral therapy.
- If the subject is clinically stable, pembrolizumab dosing may be interrupted for up to 12 weeks. Subjects should undergo weekly laboratory tests including: AST, ALT, ALP, Tbil, Dbil, INR, HBsAg, HBV DNA (if detected at the onset of the flare). Obtain anti-HBe antibody, anti-HBs antibody, and HBV DNA levels (if not detected at the onset of the flare) every 2-3 weeks.
- If ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and subjects are clinically stable, subjects may restart pembrolizumab treatment. If these conditions are not met, then pembrolizumab treatment should be permanently discontinued.

Hepatitis C Recurrence or Flare

Subjects who achieved SVR 12 and subjects with ongoing HCV infection are eligible for enrollment. In rare circumstances, HCV subjects who achieve SVR 12 may relapse at later time points. Relapse is characterized by detection of HCV RNA, often accompanied by ALT elevations to >5×ULN. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (ie, limited/no elevations of bilirubin/ALP).

Among subjects with uncontrolled hepatitis C, virologic flares are possible. Hepatitis C flares are characterized by rapid elevations of ALT and AST to >5×ULN and/or >3× baseline along with a rise in HCV RNA. ALT elevation to ≥10×ULN and a 1 log elevation in HCV RNA level are common. In the absence of hepatic decompensation, ALT/AST elevations are

typically isolated (ie, limited/no elevations of bilirubin/ALP). Laboratory abnormalities secondary to flare or recurrence are typically observed for 3-5 weeks.

Guidelines for subjects with recurrent HCV infection or an HCV flare are described below:

Recurrent HCV infection

If the subject entered the study with an HCV RNA test of "Target not Detected" and has confirmed detectable HCV RNA (2 specimens, 1 week apart), then the subject has experienced a late HCV relapse or a recurrent infection.

- Question the subject about use of injection or inhalation drugs
- At the time of first detection of HCV RNA, send a specimen for HCV genotyping
- Measure AST, ALT, ALP, Tbil, Dbil, and INR weekly
- Measure HCV RNA levels every 2 weeks
- Please discuss risk-benefit with Sponsor prior to starting HCV anti-viral therapy.

HCV Flare

- At the time of first detection of HCV RNA, send a specimen for HCV genotyping
- Measure AST, ALT, ALP, Tbil, Dbil, INR weekly
- Measure HCV RNA levels every 2 weeks
- Please discuss risk-benefit with Sponsor prior to starting HCV anti-viral therapy.

For both recurrent infection and HCV flare: if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the subjects are clinically stable, subjects may restart pembrolizumab treatment. If these conditions are not met, then pembrolizumab treatment should be permanently discontinued.

<u>Immune-related hepatitis</u>

Description: Immune-related hepatitis due to pembrolizumab should be suspected if:

- AST or ALT baseline values are less than 2×ULN, and AST or ALT laboratory values increase to ≥5×ULN
- Among subjects with baseline ALT or AST ≥2×ULN, levels increase to >3× the baseline level
- AST/ALT >500 U/L regardless of baseline level
- Among subjects with baseline Tbil levels <1.5 mg/dL: a value of >2.0 mg/dL
- Among subjects with baseline Tbil levels that are ≥1.5 mg/dL: a value of ≥2× the baseline level, OR
- Total bilirubin >3.0 mg/dL regardless of baseline level.

Immune-related hepatitis is a diagnosis made after excluding other possible etiologies for the change. Viral flare (if applicable), biliary or vascular obstruction, infection, medications, and alcohol use must be ruled out (see below).

Management

- Interrupt pembrolizumab treatment and alert the sponsor as per events of clinical interest criteria above for ALT, AST, bilirubin, and hepatic decompensation.
- Start IV corticosteroid (methylprednisolone 125 mg) followed by oral corticosteroid (1-2 mg/kg/day). Steroid taper should be started and continued for 28 days until symptoms improve to Grade 1 or less.
- Monitor with biweekly laboratory tests including AST, ALT, Tbil, Dbil, ALP, and INR.
- If symptoms and laboratory tests resolve to Grade ≤1 or baseline (if abnormal at baseline), taper steroids over 28 days. Pembrolizumab treatment may be restarted after steroid treatment has been tapered to prednisone ≤10 mg/day (or equivalent dose of another agent). Treatment and laboratory results must be reported on a CRF.
- If laboratory abnormalities do not resolve within 3 weeks, or steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks, or subjects show evidence of decompensation to CP C status or have esophageal or variceal bleeding at any point, treatment must be permanently discontinued. This must be reported on a CRF.

Other Hepatic Events of Clinical Interest

- Infection needs to be ruled out with cultures of blood, urine, and ascites (if possible), as well as chest x-ray and abdominal imaging if relevant. If an infection is found, antibiotics should be started.
- If Tbil is elevated above imaging should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.
- A careful review of drugs, including herbal and alternative medications, should be obtained, and alcohol use should be ruled out. See Section 9.4.7.2.1 for drugs which may interfere with hepatic function.
- For all of these cases, subjects may resume pembrolizumab treatment if they are clinically stable after appropriate therapy or discontinue the causative agent, as long as laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade within 3 weeks. Dose interruption of pembrolizumab is allowed up to 12 weeks at most, and discussion with sponsor is needed before restarting pembrolizumab.
- Treatment must be permanently discontinued if the subject is off pembrolizumab therapy for infection, obstruction, or drug/alcohol-related toxicity for more than 3 weeks, or if they have esophageal bleeding, or become CP C at any point.

9.4.1.4 Supportive Care Guidelines for Lenvatinib

9.4.1.4.1 MANAGEMENT OF HYPERTENSION

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

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.

Per Amendment 03, if BP is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), BP measurement should be repeated at least 5 minutes apart. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) is confirmed on 2 assessments a minimum of 30 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, appropriate antihypertensive therapy should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is first observed on 2 assessments a minimum of 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists. 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 antihypertensive 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 at least 30 minutes:

- Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving antihypertensive medication.
- For those subjects already on antihypertensive medication, the dose of current agent may be increased, if appropriate, 1 or more agents of a different class of antihypertensive should be used.
- 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 lenvatinib.

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:

- Grading according to CTCAE v4.03 will be based on the 24-hour urinary protein result if one has been obtained. Grade 3 proteinuria must be confirmed by 24-hour urine protein. Management of lenvatinib administration will be based on the grade of proteinuria according to the "Lenvatinib Dose Reduction and Interruption Instructions".
- A 24-hour urine collection initiated as soon as possible and at least within 72 hours or an immediate spot urine protein-to-creatinine ratio [UPCR] test to verify the grade of proteinuria for protein quantitation is required in the following situations:
  - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on lenvatinib
  - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
  - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is 3+ or 4+
- A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.
- Urine dipstick testing for subjects with proteinuria ≥2+ should be performed every 2 weeks (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

In the event of nephrotic syndrome, lenvatinib must be discontinued.

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, lenvatinib 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 lenvatinib must be discontinued. If a subject experiences an arterial thromboembolism event of any grade, lenvatinib 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 Rescue Medications and Supportive Care for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of non-hepatic drug-related adverse events with potential immunologic etiology are outlined in Table 4 in Section 9.4.1.3.2. 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.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 9.4.1.3.2 for guidelines regarding dose modification and supportive care.

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

- 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: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of		

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
drug administration.		

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.

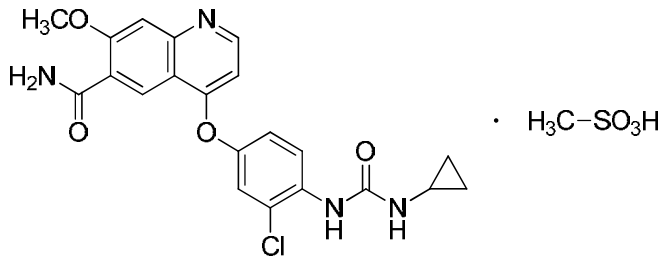
Lenvatinib will be provided as 4-mg capsules. Lenvatinib is formulated with calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, and talc.

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 11 for KEYTRUDA® package insert.)

9.4.2.3 Labeling for Study Drug

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

9.4.2.4 Storage Conditions

Study drugs will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, 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

The starting dose of lenvatinib will be 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg). This dose setting is based on the review of the safety and pharmacokinetic data derived from the Phase 1/2 study of lenvatinib in subjects with HCC (E7080-J081-202), which is adopted in the ongoing Phase 3 study of lenvatinib monotherapy in subjects with unresectable HCC (E7080-G000-304). While the recommended dose for the Phase 2 part was determined to be 12 mg for HCC subjects with CP-A based on the results of Phase 1 part, however, in order to reduce the number of dose reductions and withdrawals due to AEs within the first treatment cycle, a weight-based dosing schedule has been established with the 2 categories of 12 mg QD (BW ≥60 kg) and 8 mg QD (BW <60 kg).

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 profiles in other solid tumors. The safety of single agent pembrolizumab in subjects with

HCC is being investigated; the studies of Phase 2 (MK-3475-224/KEYNOTE-224) and Phase 3 (MK-3475-240/KEYNOTE-240) for previously systemically treated advanced HCC are ongoing (Clinicaltraials.gov; KEYNOTE-224, KEYNOTE-240).

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 in the subjects of DLT evaluation part) 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 in the subjects of DLT evaluation part.

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.

Nonsteroidal antiinflammatory drugs (NSAIDs), and low-molecular-weight heparin (LMWH) are permissible but should be used with caution. 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 8 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, 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 this study:

- Anticancer therapies such as chemotherapy, tyrosine kinase inhibitors (TKIs), local therapy, antitumor interventions (surgical resection, thoracocentesis, etc.), or immunotherapy other than study drugs
- 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.
- 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. The use of steroids in prophylaxis of allergic reaction by CT contrast agents will be allowed.
- Antiplatelet agents, factor X inhibitors, and anticoagulants that require INR monitoring, such as warfarin. (Treatments that do not require INR monitoring, such as low molecular weight heparin are permitted.)

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.

It is important for investigators to review each medication (prescription and non-prescription) the subject is taking before starting the study and at each study visit.

- At each visit, subjects should be questioned about any new drug they are taking.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.
- Drugs known to be hepatotoxic (ie, drugs with a warning of hepatotoxicity in the package insert) should be avoided during the dosing period. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nih.gov website.

Listed below are specific restrictions for concomitant therapy during the course of the study. The following medications/therapies should be avoided during the dosing period and for 14 days thereafter:

<u>Known hepatotoxic drugs, including but not limited to</u>:

- Etifoxine
- Isoniazid
- Nitrofurantoin

- Ketoconazole
- Amiodarone
- Phenytoin

Herbal Supplements/Alternative Medicines

- No herbal supplements or alternative medicines are allowed during this study.

The Exclusion Criteria describes other medications that are prohibited in this clinical study. See the related Exclusion Criteria regarding antiviral therapy for HBV and HCV.

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

- Thyroid hormone suppressive therapy (including therapy to treat hypothyroidism and hyperthyroidism)
- Adjuvant hormonal therapy for history of definitively treated breast or prostate cancer
- Anticoagulants that do not require INR monitoring, such as low molecular weight heparin
- 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 or denosumab
- 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

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the pharmacist or its designee) until the following documentation has been received by the sponsor:

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

- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the principal investigator including a copy of the principal investigator's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

The investigator and the study staff (or if regionally required, 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 GCP guidelines as well as local or regional requirements.

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

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

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority. As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the pharmacist or its designee) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and

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

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

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race and ethnicity. Baseline characteristics will include ECOG-PS, New York Heart Association (NYHA) cardiac disease classification, BCLC staging, and tumor-node-metastasis (TNM) staging at initial diagnosis (Appendix 3, Appendix 5, Appendix 7, and Appendix 9); macroscopic invasion, extra hepatic spread, and Child-Pugh score (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 and current medical conditions must be noted in the Medical History and Current Medical Conditions CRF.

The following disease characteristics will also be investigated:

- Cause of HCC (hepatitis B, C, alcohol, other, unknown)
- Specify whether disease is confined to liver or metastatic, and if metastatic, to which organs
- Presence and severity of any symptoms/conditions associated with HCC
- Detailed medical history of HCC including:
  - Pathology, if available
  - Date of diagnosis
  - Child-Pugh category at enrollment (Appendix 4)
  - Any surgical procedures
  - Prior treatments administered (including dates and modality)

- Hepatic intra-arterial chemotherapy
- Transarterial [chemo] embolization
- Radiofrequency ablation
- Cryoablation
- Percutaneous ethanol injection
- Other treatments

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

9.5.1.2.2 GASTROENTEROLOGICAL ENDOSCOPY

Gastroenterological endoscopy will be performed at Screening only. Gastroenterological endoscopy at Screening Period is necessary only if more than 3 months have passed since the previous assessment.

9.5.1.3 Efficacy Assessments

All efficacy endpoints, other than OS, will be based on tumor assessments performed by the investigators using **mRECIST for HCC** (Lencioni and Llovet, 2010; see Appendix 2 for further details)**.** All scans for tumor assessments performed during the study should be archived in accordance with the standard local practice. The scans from subjects for DLT evaluation must be accessible in the event of a sponsor request to submit them for central review. For the Expansion part, images acquired for tumor assessments will be sent to an imaging core laboratory (ICL) for archiving and potential independent analysis including **RECIST 1.1** (Eisenhauer, et al., 2009) and mRECIST for HCC. As of Amendment 03, images acquired for tumor assessments both in DLT evaluation part and Expansion part will be sent to an ICL for archiving and independent analysis.

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

Screening tumor assessments using triphasic liver CT/MRI (optimized for pre-contrast, arterial, and portal venous phase), contrast-enhanced CT of the chest, and contrast-enhanced

CT or MRI of abdomen, pelvis, and other areas of known disease plus suspected disease should be performed within 28 days prior to C1D1.

Screening CT of the brain with contrast or MRI of the brain pre- and post-gadolinium should be performed within 28 days prior to C1D1. During the Treatment Phase and the Extension Phase, CT/MRI of the brain should be performed if clinically indicated. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability.

During the Treatment Phase and Extension Phase, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease at Screening plus newly suspected disease should be performed every 6 weeks (±1 week, starting from the date of C1D1) until Week 24 and every 9 weeks thereafter, or sooner, if clinically indicated. The same methodology (CT or MRI) and scan acquisition techniques including use and timing of IV contrast should be used as for the screening assessments. Tumor assessment at the Off-Tx Visit is only necessary if more than 4 weeks have passed since the previous assessment (window for these assessments is within 1 week of the Off-Tx Visit).

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.

All subjects are required to undergo chest, abdomen, and pelvis imaging at baseline and at all follow-up time points. Contrast-enhanced CT of the chest and contrast-enhanced CT or MRI of the abdomen, pelvis, and any other areas of disease, as clinically indicated, will be acquired at Screening and at all imaging time points. Liver CT or MRI must be performed using triphasic scanning technique optimized to capture pre-contrast, arterial, and portal venous phase. Contrast-enhanced CT or MRI (pre-and post-gadolinium) of the brain will be acquired at Screening and as clinically indicated.

Treatment decisions by the investigator will be based on mRECIST for HCC. If the time point tumor assessment is progressive disease (PD) per mRECIST, the investigator will consider whether the subjects should discontinue from study treatment. The decision to continue study treatment after the initial progression per mRECIST is at the investigator's discretion based on the clinical status of the subject. Subjects will be considered to discontinue study treatment upon evidence of further radiologic progression as judged by the investigator. However, subjects will be permitted to continue treatment beyond initial progression per mRECIST as long as the investigator judges that the subject is clinically stable and still receiving clinical benefit and is tolerating study drug treatment. Clinically stable is 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

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

In order for stable disease (SD) 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 of (partial response [PR] or complete response [CR]) should be confirmed no less than 4 weeks after the initial response, but generally at the next scheduled tumor assessment time point.

Discontinuation of pembrolizumab treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab beyond the date when the initial CR was declared.

Subjects will be followed-up every 12 weeks (±1 week) for survival and subsequent anticancer treatments as long as the subject is alive and/or until completion of the primary analysis, unless the subject withdraws consent or the sponsor terminates the study. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email. All anticancer therapy will be recorded until time of death or termination of survival follow up.

9.5.1.3.1 TUMOR IMAGING DURING SECOND COURSE PHASE (PEMBROLIZUMAB RETREATMENT)

Tumor imaging using the same methodology as during the initial treatment phase must be performed within 28 days prior to restarting treatment with pembrolizumab ± lenvatinib. Tumor assessments should then be performed by the investigator at a frequency according to the local standard of care, but not less frequently than every 12 weeks. During the Second Course (Pembrolizumab Retreatment) Phase, scans will no longer be sent to the imaging core lab.

For subjects who discontinue pembrolizumab ± lenvatinib in the Second Course Phase, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For subjects who discontinue study treatment because of documented disease progression, this is the final required tumor imaging.

For subjects who discontinue pembrolizumab ± lenvatinib in the Second Course Phase without documented disease progression, the investigator should make every effort to continue monitoring their disease status as clinically indicated thereafter until the subject either starts a new anticancer treatment, has disease progression, withdraws consent, or dies, or the study ends, whichever occurs first.

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 9).

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 9. Table 6 presents the detailed blood sampling schedule for pharmacokinetic assessments. As of Amendment 03, the enrollment for Expansion part may be further expanded up to approximately 94 evaluable subjects. For the subjects in Expansion part added as of Protocol Amendment 03, blood samples for lenvatinib will be collected as the sparse sampling scheme (Table 6). 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. For the subjects in Expansion part added as of Protocol Amendment 03, the actual time, date, and dose of lenvatinib administered on Day 1 of Cycle 2, 4, 6, and the day before of Day 1 of Cycle 2, 4 and 6 will be additionally 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 6 Blood Sampling Schedule for Pharmacokinetic Assessments

Lenvatinib – Subjects Enrolled in DLT Evaluation Part and Expansion Part as per Original Protocol, Amendment 01, and Amendment 02

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

Lenvatinib Sparse Sampling for the Subjects in Expansion Part as per Amendment 03 Onwards

Days	Time (on each Day)
C1D1	0.5-4 h post dose of lenvatinib
	6-10 h post dose of lenvatinib
C1D15	Predose of lenvatinib
	0.5-4 h post dose of lenvatinib
	6-10 h post dose of lenvatinib
Day 1 of Cycles 2, 4 and 6	Predose of pembrolizumab

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 9. Table 7 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 7 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
C6D1	Predose of pembrolizumab	≤24 h before infusion

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 9).

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 predose on Day 1 of subsequent cycles up to and including Cycle 18, and at the off-treatment assessment. Subjects will provide an archival tumor tissue sample and/or a fresh biopsy of tumor before treatment for biomarker analyses (see the Inclusion Criteria). 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 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-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-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 tumor biopsies will be collected from consented subjects to examine markers including markers of target engagement, relevant pharmacodynamic biomarkers, and potential markers of response.

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 predose on C1D15 and Day 1 of subsequent cycles up to and including Cycle 18 and at the off-treatment assessment. Cf-nucleic acids 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 outcomes 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.

Data will be used to explore pharmacokinetics/pharmacodynamic (PK/PD) relationships for effects of lenvatinib in combination with pembrolizumab on ORR, other efficacy-related parameters including PFS and OS, AEs/dose reductions, and blood-borne and tumor biomarkers. Exploratory/graphical analyses will be conducted for PK/PD evaluations and may be followed by model-based analyses. PK/PD results will be provided in a separate report.

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 laboratory tests including 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 9.

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 recorded 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 until 30 days after the last dose of study treatment. Serious AEs regardless of causality assessment must be collected through the last visit and for 120 days after the subject's last dose or for 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. An AE will not be recorded on the Adverse Event CRF if other anticancer treatment is started. All SAEs will be recorded 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 6). 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. Hepatic events of clinical interest include any of the following events. All of these events will require holding pembrolizumab, notification of the event(s) to the sponsor within 24 hours via electronic media or paper (see Section 9.5.4.3.2), and a hepatology consultation.

For dose interval modification and guidance related to the diagnosis and management of hepatic events of clinical interest, refer to **Guidance for Management of Hepatic Events of Clinical Interest** of Section 9.4.1.3.2.

a. ALT:
   i. Among subjects with baseline ALT <2×ULN: ALT ≥5×ULN

ii. Among subjects with baseline ALT ≥2×ULN: ALT >3× the baseline level

iii. ALT >500 U/L regardless of baseline level

b. AST:

i. Among subjects with baseline AST <2×ULN: AST ≥5×ULN

ii. Among subjects with baseline AST ≥2×ULN: AST >3× the baseline level

iii. AST >500 U/L regardless of baseline level

c. Total Bilirubin:

i. Among subjects with Baseline levels <1.5 mg/dL: a value of >2.0 mg/dL

ii. Among subjects with Baseline levels that are ≥1.5 mg/dL: a value ≥2× the baseline level

iii. Total bilirubin >3.0 mg/dL regardless of baseline level

d. Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:

i. New onset ascites uncontrollable with diuretic

ii. Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)

iii. Hepatic Encephalopathy

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 recorded 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 8. The Schedule of Procedures/Assessments (Table 9) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. 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 8 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential INR[a]
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[b]	TSH, free T4 levels and T3 or free T3 levels
Other	Albumin, cholesterol, glucose, lactate dehydrogenase, total protein, triglycerides Pregnancy test (serum or urine β-hCG)[i]
Urinalysis[f]	Glucose, ketones, pH, protein, blood (or hemoglobin), specific gravity, UPCR[h]
Other	Ammonia[c], HIV Ab[c], HCV Ab[c], HBsAg[c], HBV DNA[d] α-fetoprotein (AFP)[e] Amylase[g], lipase[g]

C#D# = Cycle #/Day #, RBC = red blood cell, WBC = white blood cell, HBcAb = hepatitis B core antibody, HBsAg = hepatitis B surface antigen, HBsAb = hepatitis B surface antibody, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV Ab = human immunodeficiency virus antibody, INR = International Normalized Ratio, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid stimulating hormone, UPCR urine protein-to-creatinine ratio.

a: INR will be assessed on C2D1 and every cycle Day 1 thereafter.
b: TSH and free T4 will be assessed at Screening, Baseline, C3D1 and every 2 cycles thereafter (C5D1, C7D1, etc) and Off-Treatment Visit. T3 or free T3 levels will be assessed at Screening and Baseline.
c: Only at Screening.
d: Subjects who are HBsAg (+), or anti-HBcAb (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA need monitoring with HBV DNA every 3 weeks during study treatment.
e: α-fetoprotein (AFP) will be measured on C2D1, C3D1, and every 2 cycles thereafter.
f: 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.

Table 8 Clinical Laboratory Tests

Category	Parameters

g: Amylase and lipase will be measured at Screening, C2D1 and every cycle thereafter.
h: UPCR will be measured as needed.
i: Subjects must have a pregnancy test prior to administration/dispensing of pembrolizumab/lenvatinib at the beginning of each treatment cycle.

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

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. 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 9) 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. As of Amendment 03, for subjects with an elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), BP measurement should be repeated at least 5 minutes apart. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. Elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) is confirmed on 2 assessments a minimum of 30 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 9). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a neurological examination. 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 9). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3×4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position or sitting for a period of 5 minutes prior to the ECG.

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 MULTIGATED 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 9). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF.

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.

9.5.1.6 Other Assessments

For the subjects in Expansion part added as of Protocol Amendment 03, assessments of HRQoL scores will be performed using the generic cancer HRQoL instrument (EORTC QLQ-C30), the HCC-specific module (EORTC QLQ-HCC18) (Blazeby, et al., 2004), and the generic HRQoL instrument, EQ 5D-5L. Subjects will be asked to complete each of the three questionnaires at the Baseline Visit, on Day 1 of each subsequent cycle, and at the Off-Treatment Visit. Validated translations of questionnaires will be used according to EORTC and FDA guidelines. Assessments will be performed in English or in the validated local language, where available. The subject will complete HRQoL questionnaires. Site personnel should check the forms returned by the subject for completeness before the subject leaves the clinic. If the subject is unable to complete the form, qualified site personnel may administer the questionnaires via interview and complete the forms for the subject.

The EORTC QLQ-C30 is a 30-item validated questionnaire that is used in assessing HRQoL in cancer patients within the context of clinical trials. The EORTC QLQ-HCC18 is a 18-item validated questionnaire that was developed to assess health-related quality of life among

patients with hepatobiliary cancers. In both assessments, there are four scale scores: 1) Not at all, 2) A little, 3) Quite a bit, and 4) Very much.

EQ-5D-5L is a standard instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 9 present the schedule of procedures and assessments for the study. Table 10 presents the schedule of procedures/assessments for the Second Course (Pembrolizumab Retreatment) Phase for the study.

Table 9 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])**		**Treatment (Cycle 3[b] & Beyond)**		**Follow-up Period**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12, etc.**	**9, 11, 13, etc.**	**Off-Treatment Visit[v]**	**Follow-up**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	1	15	Within 30 days after last dose	Every 12 weeks[y]
	Assessments											
S	Informed consent	X										
S	Inclusion/exclusion	X	X									
S	Demographic data	X										
S	ECOG-PS/NYHA[c]	X	X				X		X		X	
NS	BCLC staging/TNM staging	X										
NS	Medical/surgical history	X	X									
S	Prior medications	X										
NS	Gastroenterological endoscopy[p]	X										
NS	Viral tests at Screening (HIV Ab, HCV Ab, HBsAg) [aa]	X										
NS	HBV DNA[bb]	X		X			X		X			
S	Vital signs[d]	X	X	X	X	X	X	X	X	X[w]	X	
-	Physical examination[e]	X	X[f]	X	X	X	X	X	X		X	
NS	12-lead ECG[g]	X		X			X		X		X	

Table 9 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])**		**Treatment (Cycle 3[b] & Beyond)**		**Follow-up Period**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12, etc.**	**9, 11, 13, etc.**	**Off-Treatment Visit[v]**	**Follow-up**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	1	15	Within 30 days after last dose	Every 12 weeks[y]
	Assessments											
S	MUGA or echocardiogram[x]	X		X								

Table 9 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])**		**Treatment (Cycle 3[b] & Beyond)**		**Follow-up Period**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12, etc.**	**9, 11, 13, etc.**	**Off-Treatment Visit[v]**	**Follow-up**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	1	15	Within 30 days after last dose	Every 12 weeks[y]
	Assessments											
S	Clinical chemistry & hematology[h, cc]	X	X		X	X	X	X	X		X	
S	Thyroid function tests[h, cc]	X	X						X[h]		X	
S	Urinalysis (Dipstick)[i, cc]	X	X		X	X	X	X	X	X[w]	X	
S	Pregnancy test[j, cc]	X	X				X		X		X	
S	Blood coagulation test (INR)[h,cc]	X	X				X		X		X	
NS	α-fetoprotein (AFP)[z]	X					X		X		X	
NS	Ammonia test	X										
NS	Child-Pugh score	X	X[ee]				X		X		X	
NS	HRQoL[gg] (For the subjects in Expansion part added as of Amendment 03)		X				X		X		X	
NS	Amylase and lipase	X					X		X		X	
S	Lenvatinib treatment			Throughout								

Table 9 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])**		**Treatment (Cycle 3[b] & Beyond)**		**Follow-up Period**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12, etc.**	**9, 11, 13, etc.**	**Off-Treatment Visit[v]**	**Follow-up**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	1	15	Within 30 days after last dose	Every 12 weeks[y]
	Assessments											
NS	Pembrolizumab treatment[dd]			X			X		X			
NS	Lenvatinib PK blood samples[k]			X		X						
NS	Lenvatinib PK blood samples[ff] (For the subjects in Expansion part added as of Amendment 03)			X		X	X		X[ff]			
NS	Pembrolizumab PK blood samples[l]			X[l]			X[l]		X[l]		X	

Table 9 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])**		**Treatment (Cycle 3[b] & Beyond)**		**Follow-up Period**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12, etc.**	**9, 11, 13, etc.**	**Off-Treatment Visit[v]**	**Follow-up**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	1	15	Within 30 days after last dose	Every 12 weeks[y]
	Assessments											
NS	Anti-pembrolizumab antibodies (ADA) blood samples[m]			X[m]					X[m]			
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 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 disease progression. Responses must be confirmed at least 4 weeks later (usually at the next tumor assessment time point). Triphasic CT/MRI of liver is mandatory at Screening and all subsequent time points unless it becomes medically contraindicated. All subjects continuing study treatment after initial mRECIST for HCC-defined progression must continue tumor assessments at the same interval (and have copies of all tumor assessments sent to the ICL) until further progression and/or loss of clinical benefit as judged by the investigator.								
NS	CT or MRI of the brain[o]	X		Brain scans will be performed if clinically indicated and within 1 week of subject achieving CR.								
S	Archival tumor block or slides[q, t]	X[q]										
S	Fresh Tumor Biopsies (additional consent required) [r]	X[r]										
S	Blood sample (serum) for biomarkers[s]			X		X	X		X		X	

Table 9 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])**		**Treatment (Cycle 3[b] & Beyond)**		**Follow-up Period**	
	Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 10, 12, etc.**	**9, 11, 13, etc.**	**Off-Treatment Visit[v]**	**Follow-up**
	Day	–28 to –3	–3 to –1	1	8	15	1	15	1	15	Within 30 days after last dose	Every 12 weeks[y]
	Assessments											
S	Biomarker (plasma) sample[s]			X		X	X		X		X	
S	Biomarker (whole blood) sample[s]			X		X	X		X		X	
S	Concomitant medications/therapies[u]	Throughout										X
S	AEs/SAEs[u]	Throughout										
S	Survival[y]	Throughout										

ADA = anti-drug antibody, AE = adverse event, BCLC = Barcelona Clinic Liver Cancer, BP = blood pressure, C#D# = Cycle #/Day #, CRF = case report form, CR = complete response, CT = computed tomography, DLT = dose-limiting toxicity, ECG = electrocardiogram, ECOG-PS = Eastern Cooperative Oncology Group Performance Status, HBcAb = hepatitis B core antibody, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HIV Ab = human immunodeficiency virus antibody, ICL = imaging core laboratory, INR = international normalized ratio, 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, T3 = triiodothyronine, 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 30 minutes apart. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart.
e. A comprehensive physical examination (including a neurological examination) will be performed at the Screening or Baseline Visit, on C1D15, on Day 1 of each subsequent cycle, and at the Off-Treatment Visit assessment. A symptom-directed physical examination will be performed on C1D1, C1D8, 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 min 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). TSH and free T4 will be assessed at Screening, Baseline, C3D1 and every 2 cycles thereafter (C5D1, C7D1, etc.) and Off-Treatment Visit.T3 or free T3 levels will be assessed at Screening and Baseline.
i. Urinalysis will be performed at Screening, Baseline, C1D8, C1D15, and each study visit of every cycle thereafter. Urinalysis will include glucose, hemoglobin (or blood), ketones, pH, protein, specific gravity. If urinalysis suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity test should be performed at the institution's laboratory. If urine protein is ≥2+ on urinalysis, then see Footnote W.
j. A serum and/or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months).
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 and 6.
n. Pretreatment Phase: Tumor assessments using triphasic liver CT/MRI (optimized for pre-contrast, arterial phase, and portal venous phase), contrast-enhanced CT of the chest, and contrast-enhanced CT or MRI of the abdomen, pelvis, and other areas of known disease plus suspected disease should be performed within 28 days prior to C1D1.
Treatment/Extension Phase: Tumor assessments using triphasic liver CT/MRI (optimized for pre-contrast, arterial phase, and portal venous phase), contrast-enhanced CT of the chest, and contrast-enhanced CT or MRI of the abdomen, pelvis, and other areas of known disease at Screening plus newly suspected disease should be performed as indicated in the Schedule of Procedures/Assessments above (or sooner if there is evidence of progressive disease). The same methodology (CT or MRI) and scan acquisition techniques should be used as for the screening assessments. Objective responses must be confirmed at least 4 weeks later (eg, generally at the next tumor assessment time point).
Follow-up Period: Subjects who discontinue treatment without disease progression should continue tumor assessments (every 6 weeks until Week 24, then every 9 weeks as needed) until disease progression or beginning another anticancer therapy. All subjects continuing study treatment after initial mRECIST for HCC-defined progression must continue tumor assessments at the same interval (and have copies of all tumor assessments sent to the ICL in the Expansion part) until further progression and/or loss of clinical benefit as judged by the investigator.
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 within a target of 1 week after a subject achieves a CR. The same methodology and scan acquisition techniques used at Screening should be used throughout the study to ensure comparability.
p. Gastroenterological endoscopy at Screening period is necessary only if more than 3 months have passed since the previous assessment.

q. An archival tumor tissue sample should be available prior to first dose. Collection of archival tumor tissue or a newly obtained biopsy prior to the first dose of study treatment will be required in Expansion cohort, while it will be optional in the patients who are not enrolled in Expansion cohort. 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 tumor biopsies will be collected at the Screening visit 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 time points: 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 should be obtained prior to the first dose of study treatment. 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 without archival tumor tissue and with inaccessible tumors for biopsy specimens can be enrolled without a biopsy. 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.

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. Assessments/procedures on Day 15 of Cycle 3 or later can be skipped only if subject's safety is assured by 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 every 2 weeks (on Day 1 and Day 15 or more frequently as clinically indicated until the results have been 1+ or negative for 2 consecutive treatment cycles). If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 1 and Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 2 consecutive treatment cycles.
Subjects will visit on 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: Subjects will be followed-up every 12 weeks (±1 week) for survival and subsequent anticancer treatments as long as the subject is alive and/or until completion of the primary analysis, unless the subject withdraws consent or the sponsor terminates the study. If a clinic visit is not feasible, follow-up information may be obtained via telephone or email. All anticancer therapy will be recorded until time of death or termination of survival follow up.

z: α-fetoprotein (AFP) will be measured at the Screening Visit, on C2D1, C3D1, every 2 cycles thereafter (C5D1, C7D1, C9D1, etc.), and at the Off-Treatment Visit.

aa: Viral tests of HIV Ab, HCV Ab and HBsAg (quantitative assay, High-sensitivity) will be done at the Screening visit.

bb: Subjects who are HBsAg (+), or anti-HBcAb (+) and/or anti- HBsAb (+) but negative for HBsAg and HBV DNA need monitoring with HBV DNA every 3 weeks during study treatment.

cc: All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to pembrolizumab administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle. Monitor subjects with Grade 4 thrombocytopenia every 48 hours until resolution to baseline or Grade 1.

dd: Pembrolizumab will be administered until 2 years after C1D1 at the latest. 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 in the subjects of DLT evaluation part) 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 in the subjects of DLT evaluation part.
Note: Subjects who stop study treatment after receiving 35 administrations of pembrolizumab for reasons other than progressive disease (PD) or intolerability, or subjects who attain a complete response (CR) and stop study treatment, may be eligible to receive up to 17 additional administrations of pembrolizumab (approximately 1 year). This will be a second course of treatment (see Table 10 for details).

ee: Data of C1D1 can be used for Baseline if it is assessed before treatment of study drugs.
ff: For the subjects in Expansion part added as of Amendment 03, study Treatment PK blood samples drawn 0.5-4 hours, and 6-10 hours post lenvatinib dose on C1D1, prior to dose and 0.5-4 hours, and 6-10 hours post lenvatinib dose on C1D15. Study Treatment PK blood samples drawn prior to pembrolizumab dose only on Day 1 of Cycles 2, 4, and 6.
gg: HRQoL surveys are conducted for the subjects in Expansion part added as of the protocol Amendment 03.

Table 10 Schedule of Procedures/Assessments in the Second Course (Pembrolizumab Retreatment) Phase

Phase	**Retreatment Baseline**	**Second Course Phase (Retreatment)**			
Period		**Treatment Period**			**Follow-Up Period**
Visit	100	101-998	102-997	999[n]	1000
Day	-1	**Cycle X (Last Cycle +1) and Beyond[a]**		**Off-Treatment Visit**	
		1	15		
Assessments					
Inclusion/exclusion	X				
ECOG-PS[b]	X	X		X	
Vital signs and weight[c]	X	X	X[c]	X	
Physical examination[e]	X	X	X	X	
12-lead ECG[f]	X	X		X	
MUGA scan or echocardiogram[g]	X			X	
Hematology and clinical chemistry[h]	X	X		X	
Urine dipstick testing[d]	X	X	X[d]	X	
Pregnancy test[i]	X	X		X	X
Tumor assessments: CT (MRI)[j]	X	Tumor assessments will be performed according to the local standard of care.			
Brain scan	X	Brain scans will be performed if clinically indicated.			
Survival[k]					X

Phase	Retreatment Baseline	Second Course Phase (Retreatment)		
Period		**Treatment Period**		**Follow-Up Period**
Study drug treatment		21-day cycle of lenvatinib daily plus pembrolizumab IV once every 21 days		
Concomitant medications[l]	X	Throughout	X	
AEs/SAEs[m]	X	Throughout	X	X

AE = adverse event; BP = blood pressure; BW = body weight; CBC = complete blood count; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic case report form; HR = heart rate; IV = intravenous; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; med = medication(s); MRI = magnetic resonance imaging; MUGA = multigated acquisition; RR = respiratory rate; SAE = serious adverse event; ULN = upper limit of normal; w/in = within.

a. Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in this Schedule of Procedures/Assessments.
b. For ECOG-PS assessment, see protocol appendices.
c. Assessments will include vital signs (resting BP, HR, RR, and body temperature) and BW. Only 1 BP measurement is needed for subjects with systolic BP <140 mmHg and diastolic BP <90 mmHg. If the subject's initial BP measurement is elevated (ie, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), the BP measurement should be repeated at least 5 minutes later. The mean value of 2 measurements at least 5 minutes apart is defined as 1 BP assessment. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value. Subjects with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg assessment must have their BP monitored on Day 15 (or more frequently as clinically indicated) until their systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. See Section 9.4.1.4.1, *Management of Hypertension*, for further details.
   Note: During Cycle 3 and subsequent cycles, subjects may return to the clinic for the Day 15 visit if BP monitoring is required as specified above. The Day 15 visit is mandatory in Cycles 1 and 2.
d. Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 or more frequently as clinically indicated until the results have been 1+ or negative for 2 consecutive treatment cycles. Urine dipstick testing should be performed preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the subject does not have to come for a visit to the site). If a new event of proteinuria ≥2+ occurs, the subject must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 2 consecutive treatment cycles. For subjects with proteinuria ≥2+, see Section 9.4.1.4.2, *Management of Proteinuria*, for further details.
   Note: During Cycle 3 and subsequent cycles, subjects may return to the clinic for the Day 15 visit if urine dipstick testing is required, as specified above. The Day 15 visit is mandatory in Cycles 1 and 2.

e. A comprehensive physical examination will be performed on Day 1 of each cycle and at the off-treatment assessment. A physical examination may also be performed on Day 15, or sooner if clinically indicated.
f. Single 12-lead ECG as clinically indicated. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.
g. A MUGA scan or echocardiogram will be performed during or within 1 week following the off-treatment assessment, or sooner if clinically indicated. MUGA scans or echocardiograms will be performed in accordance with the institution's standard practice. Assessment should use the same methodology (MUGA scan or echocardiogram).
h. Hematology and clinical chemistry results must be reviewed within 2 business days of receipt of results for all subsequent cycles. Assessments scheduled may be performed within 72 hours prior to the visit. If Grade ≥3 clinically significant hematologic or clinical chemistry toxicities occur, repeat laboratory tests and AE assessments at least every 3-7 days until improvement to Grade <3. For subjects with blood glucose > ULN, a fasting (>6 h, water only) blood glucose sample will be obtained.
i. A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) on Day 1 of each cycle from Cycle 2 onwards, at the Off-Treatment Visit and every 30 days up to 120 days after the last dose of the study medication or the start of a new anticancer therapy, whichever comes first.
j. Tumor imaging using the same methodology as during the initial treatment phase must be performed within 28 days prior to restarting treatment with pembrolizumab ± lenvatinib. Tumor assessments should then be performed by the investigator at a frequency according to the local standard of care, but not less frequently than every 12 weeks. During the Second Course (Pembrolizumab Retreatment) Phase, scans will no longer be sent to the imaging core lab.
k. Subjects will be followed for survival every 12 weeks (±1 week) after the Off-Treatment Visit unless they withdraw consent or are lost to follow-up. If a clinic visit is not feasible, follow up information may be obtained via telephone or e-mail.
l. Concomitant medications will be recorded for 30 days after last dose. All anticancer therapy will be recorded until time of death or termination of survival follow up.
m. All AEs will be captured for 30 days after the last dose of pembrolizumab ± lenvatinib. SAEs must be collected through 120 days after the subject's last dose of pembrolizumab ± lenvatinib, or 30 days after the last dose of pembrolizumab ± lenvatinib if the subject initiates new anticancer therapy, whichever is earlier. Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of the last dose of pembrolizumab ± lenvatinib or 30 days after the last dose of pembrolizumab ± lenvatinib if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to pembrolizumab ± lenvatinib through breastfeeding during the Second Course Phase or within 120 days of the last dose of pembrolizumab ± lenvatinib, or 30 days following the last dose of pembrolizumab ± lenvatinib if the subject initiates a new anticancer therapy, whichever is earlier, must be reported.
n. Off-treatment assessments should occur within 30 days of the final dose of pembrolizumab ± lenvatinib.

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to Table 9 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 HCC.

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 24 hours from the date the investigator becomes aware of the event.

Serious AEs regardless of causality must be collected through the last visit and for 120 days after the subject's last dose or for 30 days following the last dose if the subject initiates new anticancer therapy, whichever is earlier. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

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

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

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

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 120 days of the last study treatment or 30 days following last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. Also, any exposure to study drug through breastfeeding during study treatment or within 120 days of the last study treatment, or 30 days following the last study treatment if the subject initiates a new anticancer therapy, whichever is earlier, must be reported.

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

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

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

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

9.5.4.3 Reporting of Events Associated with Special Situations

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

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

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

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

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

9.5.4.3.2 Reporting of Events of Clinical Interest

Selected nonserious and serious adverse events are also known as events of clinical interest and must be reported to the sponsor.

For the time period beginning when the consent form is signed until enrollment, any event of clinical interest, or follow up to an events of clinical interest, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at enrollment through 30 days following cessation of treatment, any events of clinical interest, or follow up to an events of clinical interest, whether or not related to the investigational product, must be reported within 24 hours to the sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable

regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

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

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

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 9).

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

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons.

Subjects except for the Expansion part 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 or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

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

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

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

9.6.2 Clinical Data Management

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

9.7 Statistical Methods

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

9.7.1 Statistical and Analytical Plans

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

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

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

To evaluate ORR and DOR by mRECIST and RECIST 1.1 based on IIR analysis is also primary objective and primary endpoint in the Expansion part.

9.7.1.1.2 SECONDARY ENDPOINTS

In DLT evaluation part, the secondary endpoints related to the efficacy endpoints will be ORR and DOR by mRECIST (based on investigator review and IIR) and by RECIST 1.1 based on IIR.

In Expansion Part, the secondary endpoints related to the efficacy endpoints will be ORR and DOR by mRECIST based on investigator review.

The following efficacy endpoints by mRECIST (based on investigator review and IIR) and RECIST1.1 (based on IIR) are also the secondary endpoints in this study:

- Objective response rate (PFS)
- Duration of response (TTP)
- Time to response (TTR)

Overall survival (OS) is also the secondary endpoint in this study.

These efficacy endpoints are defined as follows.

- **ORR** is defined as the proportion of subjects who have BOR of CR or PR at the time of data cutoff.
- **DOR** is defined as the time from the first documentation of CR or PR to the date of first documentation of disease progression 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 or death (whichever occurs first).
- **TTP** is defined as the time from the first study dose date to the date of first documentation of disease progression.

- **TTR** is defined as the time from the date of first study dose to the date of first documentation of CR or PR.
- **OS** is measured from the start date of the Treatment Phase (date of first study dose) until date of death from any cause. Subjects who are lost to follow-up and the subjects who are alive at the date of data cutoff will be censored at the date the subject was last known alive or the cut-off date, whichever comes earlier.

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

Serum ADA will be measured.

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints related to the efficacy endpoints will be DCR and CBR. These efficacy endpoints are defined as follows.

- **DCR** is defined as the proportion of subjects who have BOR of CR or PR or SD (minimum duration from C1D1 to SD ≥5 weeks).
- **CBR** is defined as the proportion of subjects who have BOR of CR or PR or durable SD (duration of SD ≥23 weeks).

For the subjects in Expansion part added as of Protocol Amendment 03, HRQoL will be assessed using EORTC QLQ-C30, the HCC-specific questionnaire (HCC-18), and a generic instrument EQ-5D-5L.

The QLQ-C30 core questionnaire (version 3.0) is a generic HRQoL measure for cancer patients, and comprises a global health status/QoL scale, five multi-item functional scales, three multi-item symptom scales, and single items for the assessment of symptoms and the financial impact of disease and treatment.

QLQ-HCC-18 is an 18-item HCC-specific supplemental module developed to augment QLQ-C30 and to enhance the sensitivity and specificity of HCC-related HRQoL parameters. HCC-18 contains six multi-item scales addressing fatigue, body image, jaundice, nutrition, pain and fever, as well as two single items addressing sexual life and abdominal swelling.

All of the derived scales for QLQ-C30 and HCC-18 range in score from 0 to 100. For the overall HRQoL and functioning scales, a higher score is correlated with better HRQoL, whereas a higher score represents worse HRQoL for symptom scales.

The EQ-5D-5L generic QoL questionnaire comprises of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has five levels (1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems, and (5) extreme problems. Thus, the final scoring consists of 3125 possible combinations or

health states. The utility value for each state is assigned based on a set of preference weights (tariffs) elicited from general population.

Mean (SD) of the derived functional / symptom scales according to the scoring manual and global health status scores will be summarized by treatment group at each time point. A separate pre-specified HRQoL analysis following FDA and EMEA PRO Guidelines will be performed and detailed in a separate Statistical Analysis Plan (SAP) and HRQoL report. Scoring of EQ-5D-5L and derivation of utility for health economic analysis will also be accomplished in a separate analysis and described in a separate HRQoL report.

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 (except for the Expansion part) 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 determine 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, part, 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, part, 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, BCLC staging, TNM staging, macroscopic invasion, extra hepatic spread, and Child-Pugh score.

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, part, and/or overall as appropriate. BOR will be summarized, and ORR 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, OS, TTP 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 post-baseline nadir (ie, maximum tumor shrinkage).

Data cutoff for the primary analysis will be done after all subjects in the Expansion part finish at least Cycle 8 assessment and have a tumor assessment for at least Week 24, or discontinue if before Cycle 8.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

The primary PK parameters of lenvatinib in the combination will be calculated using noncompartmental analysis and compared with historical data after a 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 subject 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/PD 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.

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, part, 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 and 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 approximately 30 subjects (N=6 to 10 for DLT evaluation part and N=20 for Expansion part) will be enrolled in this study. This is not based on statistical power considerations.

The sample size in the Expansion part is 20 evaluable subjects. The associated 2-sided 95% CIs for the ORR of 10% to 90% for 20 subjects are provided in Table 11.

As of Amendment 03, Expansion part may be further expanded up to approximately 94 evaluable subjects. For this expansion decision, 2 interim analyses will take place when 20 (6 subjects for DLT evaluation part plus 14 subjects for Expansion part) and 56 subjects (6 subjects for DLT evaluation part plus 50 subjects for Expansion part) have sufficient follow-up to be evaluated for response. The decision to expand enrollment will be based on the results of 2 interim analyses, which will spend $\beta = 0.012$ and $\beta = 0.024$ at the first and second interim analyses, respectively. The decision to expand enrollment will be assessed by mRECIST based on investigator review.

Based on an assumption of H0: 25% ORR and H1: 45% ORR, the 100-subject design with two futility analyses has approximately 96% statistical power at 2-sided $\alpha = 0.02$ (that corresponds to 1-sided $\alpha = 0.01$). At the first interim analysis (N = 20), if there are more than 5 responses, then approximately 36 additional subjects will be enrolled. At the second interim analysis (N = 56), if there are more than 16 responses, approximately 44 additional subjects will be enrolled. If there are 5 or fewer responses at the first interim analysis (N=20) or 16 or fewer responses at the second interim analysis (N=56), the sponsor may decide whether to expand enrollment based on clinical outcome (eg, DOR).

The boundaries for the decision to expand enrollment in Expansion part are presented in Table 12.

Table 11 2-Sided 95% Confidence Interval for the ORR of 10% to 90% (20 Subjects)

ORR (N=20)	95% CI
10%	(0.012, 0.317)
20%	(0.057, 0.437)
30%	(0.119, 0.543)
40%	(0.191, 0.639)
50%	(0.272, 0.728)
60%	(0.361, 0.809)
70%	(0.457, 0.881)
80%	(0.563, 0.943)
90%	(0.683, 0.988)

CI = confidence interval, ORR = objective response rate assessed by mRECIST based on investigator review.
95% CI is estimated using Clopper-Pearson method.

Table 12 Boundaries for the Decision to Expand Enrollment in the Expansion Part

Analysis Number	Cumulative β Spent	Objective Response Rate	P-value
Interim Analysis 1 (N=20)	0.012	0.258	0.933
Interim Analysis 2 (N=56)	0.024	0.301	0.376
Final Analysis (N=100)	0.041	0.351	0.020

9.7.3 Interim Analysis

As of Amendment 03, Expansion part may be further expanded up to approximately 94 evaluable subjects. For this expansion decision, 2 interim analyses will take place when 20 (6 subjects for DLT evaluation part plus 14 subjects for Expansion part) and 56 subjects (6 subjects for DLT evaluation part plus 50 subjects for Expansion part) have sufficient follow-up to be evaluated for response. The decision to expand enrollment will be based on the results of 2 interim analyses, which will spend $\beta = 0.012$ and $\beta = 0.024$ at the first and second interim analyses, respectively. The decision to expand enrollment will be assessed by mRECIST based on investigator review.

Based on an assumption of H0: 25% ORR and H1: 45% ORR, the 100-subject design with two futility analyses has approximately 96% statistical power at 2-sided $\alpha = 0.02$ (that

corresponds to 1-sided $\alpha = 0.01$). At the first interim analysis (N = 20), if there are more than 5 responses, then approximately 36 additional subjects will be enrolled. At the second interim analysis (N = 56), if there are more than 16 responses, approximately 44 additional subjects will be enrolled. If there are 5 or fewer responses at the first interim analysis (N=20) or 16 or fewer responses at the second interim analysis (N=56), the sponsor may decide whether to expand enrollment based on clinical outcome (eg, DOR).

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

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KISPLYX Summary of Product Characteristics:
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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

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

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

11.2 Adherence to the Protocol

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

11.3 Monitoring Procedures

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

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

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each 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 item(s), the data recorded directly on the CRF are to be considered source data:

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

- Sampling date for the clinical laboratory tests
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

In Japan, pembrolizumab is expected to be designated as a biologic product. The site in Japan 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, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

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

11.8 Handling of Study Drug

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

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

11.9 Publication of Results

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

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

11.10 Disclosure and Confidentiality

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

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

11.11 Discontinuation of Study

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

sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

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

11.12 Subject Insurance and Indemnity

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

12 APPENDICES

Appendix 1 American Association for the Study of Liver Diseases (AASLD) Criteria

Diagnosis of hepatocellular carcinoma is to be clinically confirmed according to AASLD practice guidelines as described in: Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-2. Available from: http://www.aasld.org/practiceguidelines.

The diagnostic algorithm is shown below.

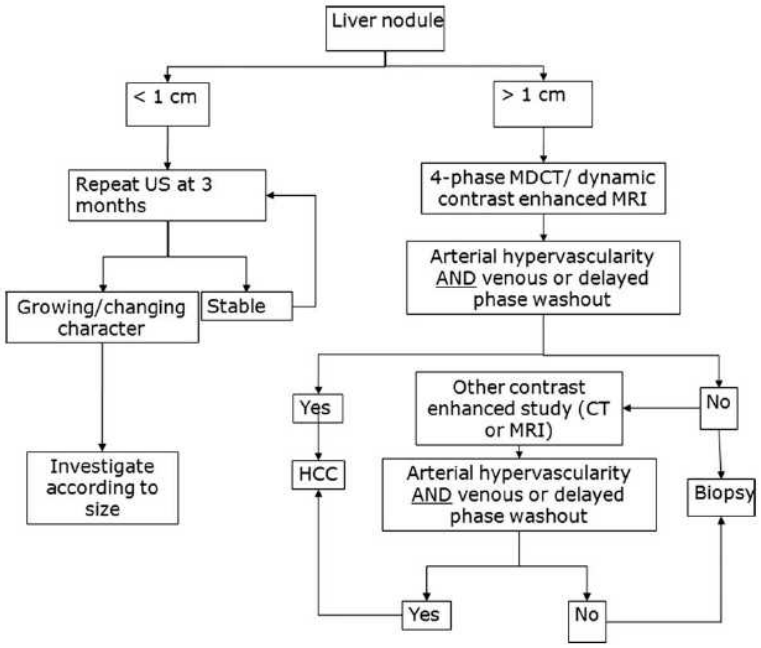

Fig. 1. Diagnostic algorithm for suspected HCC. CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound.

Appendix 2 Modified Response Evaluation Criteria in Solid Tumors (mRECIST)

Tumor response assessments in this clinical trial will use modified Response Evaluation Criteria in Solid Tumors (mRECIST) based on Lencioni and Llovet (2010) and incorporating elements of RECIST 1.1 based on Eisenhauer, et al. (2009).

QUANTITATIVE AND QUALITATIVE ASSESSMENTS OF TUMOR BURDEN

The disease burden at Baseline will be categorized into target and nontarget lesions. Within the target and nontarget categories are typical hepatic lesions, atypical hepatic lesions, and nonhepatic lesions.

- Typical hepatic lesions are lesions that display hypervascularity in the arterial phase and "wash-out" in the portal venous phase of contrast-enhanced CT or MRI imaging.
- Atypical hepatic lesions are lesions that are not showing the distinctive enhancement pattern but are considered to be malignant.
- Nonhepatic lesions are all nodal and non-nodal lesions outside of the liver.

SELECTION AND MEASUREMENT OF TARGET LESIONS

A maximum of 2 target lesions per organ and 5 target lesions in total, representative of all involved organs, may be selected. Target lesions are lesions that can be accurately measured in at least 1 dimension and whose minimum lesion size is as follows:

- Typical hepatic target lesions: The longest diameter of the viable tumor must measure ≥1 cm or ≥ two times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Atypical hepatic target lesions: The longest diameter must measure ≥1 cm or ≥ two times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Nonhepatic non-nodal target lesions: The longest diameter must measure ≥1 cm or ≥ two times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Nonhepatic nodal target lesions (lymph nodes): The short axis must measure ≥1.5 cm with exception of porta hepatis lymph nodes that need to be ≥2.0 cm in the short axis (regardless of modality/scanner type and slice thickness/reconstruction interval).

If typical and atypical liver lesions are present, preference should be given to typical liver lesions when selecting targets. Target lesions are measured at every time point and a single Sum of Diameters (SOD) will be determined by adding the longest diameters of all non-nodal lesions and short axes (ie, widest dimensions perpendicular to the long axis) of nodal nonhepatic lesions. For typical hepatic lesions the longest diameters will include only the viable tissue, while for all other target lesions all tumor tissue (whether necrotic or not) will be included in the SOD. Note that hypovascular tissue should not be considered as necrotic (nonviable) tissue. While hypovascular tissue will still show contrast uptake (although less than what would be observed in a hypervascular lesion), necrotic tissue will show complete absence of any contrast enhancement. Quantitative determinations of average Hounsfield Units (HU) in the tissue of interest both pre-contrast and post-contrast may be used, if needed, to support the subjective assessment: necrotic (nonviable) tissue will show no change in HU between the phases, while hypovascular tissue will yield an increase in HU (although less than what would be observed in a hypervascular lesion) between pre-contrast and post-contrast images of the same region. Please refer to the Image Interpretation Guidance Manual for the use of mRECIST for HCC for further details regarding differentiating hypovascular from necrotic (nonviable) tissue.

Target lesions are assessed as CR, PR, SD, PD, or NE at every time point based on the SOD.

SELECTION AND ASSESSMENT OF NONTARGET LESIONS

Nontarget lesions are all other lesions, including malignant portal vein thrombosis, infiltrative type, and diffuse type HCC with ill-defined lesion borders and truly nonmeasurable lesions. Nontarget lesions will be assessed qualitatively, and the possible assessments are CR, Non-CR/Non-PD (NN), and PD.

If a hepatic nontarget lesion exhibits an enhancement pattern that is consistent with HCC, the determination of CR, NN, PD, or NE will be dependent on the enhancing portion of the lesion. All other nontarget lesions will be assessed following the conventional RECIST 1.1 criteria.

If pleural effusions or ascites selected as nontarget lesions at Baseline are stable in size or minimally enlarging, they will be assessed as NN. A cytopathological confirmation of any effusion that appears or worsens on treatment is required when the measurable tumor has met criteria for response or SD.

NEW LESIONS

New lesions are defined as:

- Unequivocally new nonhepatic lesions seen at follow-up, without a corresponding lesion on the baseline imaging

- New typical hepatic lesions displaying intratumoral arterial enhancement (hypervascularization in the arterial phase and washout in the portal venous phase on contrast-enhanced CT or MRI) that measure ≥1 cm in the longest diameter

- New atypical hepatic lesions ≥1 cm in the longest diameter that show interval growth in subsequent scans of at least 1 cm

Any lesion that meets the requirements for unequivocal new lesions will trigger PD. Any lesion that does not meet the above criteria (eg, <1 cm in longest diameter and/or does not show typical HCC vascular enhancement pattern) should be considered an equivocal new lesion. If an equivocal lesion is later determined to be unequivocal, the time point of progression will be the time point the lesion was first noted as equivocal.

OVERALL RESPONSE ASSESSMENTS

Target Lesions	Nontarget Lesions	New Lesions	Overall Time Point Response
CR	CR	No	CR
CR	NN	No	PR
CR	NE	No	PR
PR	NE	No	PR
PR	CR	No	PR
PR	NN	No	PR
SD	NE	No	SD
SD	CR	No	SD
SD	NN	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE
CR	No nontarget lesions identified	No	CR
PR	No nontarget lesions identified	No	PR
SD	No nontarget lesions identified	No	SD

CR = complete response, NE = not evaluable, NN = Non-CR/Non-PD, PD = progressive disease, PR = partial response, SD = stable disease.

Appendix 3 Barcelona Clinic Liver Cancer (BCLC) Staging System

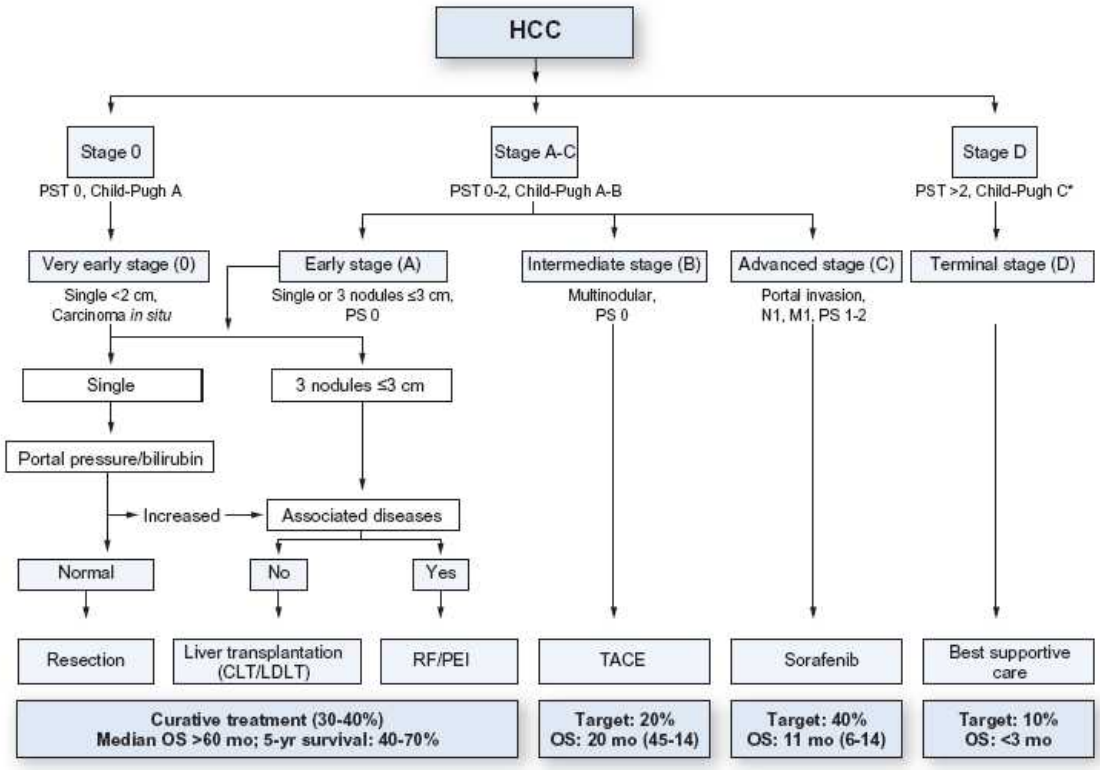

Fig. 3. Updated BCLC staging system and treatment strategy, 2011.

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European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012 Apr;56(4):908-43. Erratum to: ‘‘EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma’’ [J Hepatol 2012;56:908-43]. J Hepatol. 2012 Jun;56(6):1430.

Appendix 4 Child-Pugh Classification

Parameter	Score[a]		
	1	2	3
Ascites	Absent	Mild (Respond to treatment)	Moderate (Refractory)
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.30	>2.30
Encephalopathy[b]	0	1–2	3–4

INR = international normalized ratio.

a: Child-Pugh A: 5 or 6 points; Child-Pugh B: 7–9 points; Child-Pugh C: >9 points.

b: Encephalopathy grades defined as follows:

Grade 0: normal consciousness, personality, neurological examination, electroencephalogram

Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per second) waves

Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

Grade 4: unrousable, coma, no personality/behavior, decerebrate, slow 2–3 cps delta activity

Appendix 5 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 6 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 7 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 8 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 9 Tumor, Node, and Metastasis Staging of Hepatocellular Carcinoma

The TNM (tumor-node-metastasis) classification for staging of hepatocellular carcinoma per the American Joint Committee on Cancer (AJCC) is provided below:

Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Solitary tumor without vascular invasion

T2 Solitary tumor with vascular invasion or multiple tumors, none >5 cm

T3a Multiple tumors >5 cm

T3b Single tumor or multiple tumors of any size involving a major branch of the portal or hepatic vein

T4 Tumor(s) with direct invasion of adjacent organs other than gallbladder or with visceral peritoneum

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Anatomic stage/prognostic groups

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3a	N0	M0
IIIB	T3b	N0	M0
IIIC	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Source: Cheng CH, Lee CF, Wu TH, Chan KM, Chou HS, Wu TJ, et al. Evaluation of the new AJCC staging system for resectable hepatocellular carcinoma. World J Surg Oncol. 2011;9:114. Available from: http://www.wjso.com/content/9/1/114.

Appendix 10 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 pharmacogenomic samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the pharmacodynamic, 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 11 KEYTRUDA® Package Insert

The latest KEYTRUDA Package Insert is available in the FDA website at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125514s014lbl.pdf

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

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E7080-J081-116
Study Protocol Title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subjects with Hepatocellular Carcinoma
Investigational Product Name:	Lenvatinib (E7080/LENVIMA™) and Pembrolizumab (MK-3475/KEYTRUDA®)
IND Number:	115650
EudraCT Number:	2018-000522-55

SIGNATURES

Authors:

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21 Jan 2019
Date

Oncology Business Group, Eisai Ltd.

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22 Jan, 2019
Date

Oncology Business Group, Eisai Inc.

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INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7080-J081-116
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IND Number:	115650
EudraCT Number:	2018-000522-55

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

Medical Institution

Investigator	Signature	Date