1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7080-J081-117
Study Protocol Title:	A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112-8088 Japan Ono Pharmaceutical Co., Ltd. 1-5 Doshomachi 2-chome, Chuo-ku, Osaka 541-8564 Japan
Investigational Product Name:	E7080/lenvatinib, ONO-4538/nivolumab
Indication:	Hepatocellular carcinoma
Phase:	1b
Approval Date:	V8 05 Feb 2021
GCP Statement:	This study is to be performed in full compliance with Good Clinical Practice (GCP) and all applicable regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of 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.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7080, ONO-4538

Name of Active Ingredient: Lenvatinib, Nivolumab

Study Protocol Title

An Open-Label Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Study Regions (Country) or Sites

Part 1: 1 center in Japan

Part 2: TBD [multiple centers in Japan])

Study Period and Phase of Development

Approximately 45 months
Phase 1b

Objectives

Primary Objective

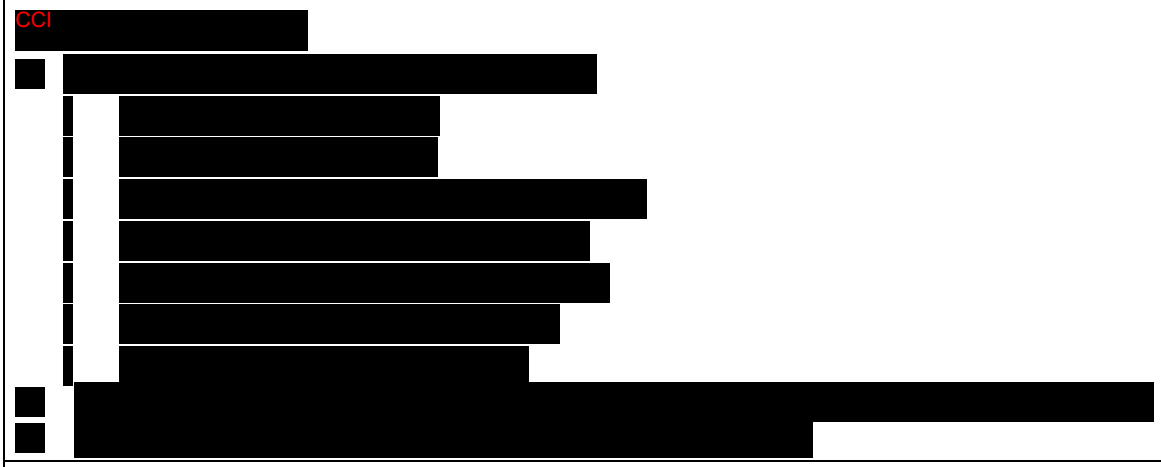
・ To evaluate the tolerability and safety for combination of lenvatinib plus nivolumab in subjects with hepatocellular carcinoma (HCC)

Secondary Objectives

・ To evaluate the following efficacy endpoints based on investigator review in subjects with HCC:

- Objective response rate (ORR)

・ To assess the pharmacokinetic (PK) profile of lenvatinib and nivolumab



Study Design

Overall Design

This study will be conducted in 2 parts (Part 1 and Part 2). Part 1 will assess the tolerability of lenvatinib in combination with nivolumab in subjects with HCC for which no other appropriate therapy is available. Part 2 is to further characterize the safety and to assess preliminary efficacy of the combination therapy in subjects with HCC with no prior systemic therapy. Part 1 and Part 2 will consist of a Pretreatment Phase, a Treatment Phase, and a Follow-up Phase. The Pretreatment Phase will involve obtaining informed consent, a screening test, and a baseline assessment. The Treatment

Phase will start on Cycle 1 Day 1 (C1D1). Each cycle is 4 weeks long and subjects will continue treatment until they meet any of the criteria in "Discontinuation Criteria by Subject". The Follow-up Phase will consist of the examinations at study discontinuation and the final observation 30 days after the final treatment.

Part 1
Study treatment and starting dose are as follows.

Lenvatinib: 12 mg (Body weight [BW] ≥60 kg) or 8 mg (BW <60 kg) once daily orally.
Nivolumab: 240 mg (every 2 weeks [Q2W], intravenous [IV]) (Days 1 and 15 of each cycle)

The tolerability will be reviewed based on dose limiting toxicity (DLT) of Cycle 1 (4 weeks) according to the following procedures and criteria.

First, 3 subjects will be enrolled.
(1)DLT occurs in 0 or 1 of 3 subjects.
Add 3 more subjects and assess in a total of 6 subjects.
1)DLT occurs in 0 or 1 of 6 subjects.
This dose level is judged to be tolerable.
2)DLT occurs in 2 or more of 6 subjects.
The tolerability with this dose level will be discussed by the sponsor, sponsor's responsible medical officer, and investigator.
(2)DLT occurs in 2 or more of 3 subjects.
The tolerability with this dose level and appropriateness of additional enrollment will be discussed by the sponsor, sponsor's responsible medical officer, and investigators.

In this dose level, at least 3 subjects treated with lenvatinib 12 mg (BW ≥60 kg) and nivolumab need to be included in the 6 subjects for DLT evaluation. If this dose level is not tolerable, upon discussions among the sponsor, sponsor's responsible medical officer, and investigator, the lower dose level of cohort will be considered or the study will be discontinued, and the protocol will be amended as necessary. An efficacy and safety evaluation advisor may be consulted for the consideration as needed.

A DLT is defined as any of the events noted in the table below considered to be at least possibly related to lenvatinib and/or nivolumab occurring during Cycle 1.

Hematologic Toxicity	• Febrile neutropenia • Grade 4 neutropenia lasting >7 days • Grade 4 thrombocytopenia • Grade 3 thrombocytopenia lasting > 7 days or associated with bleeding • Grade 4 anemia
Nonhematologic Toxicity (Hepatotoxicity)	• Clinical deterioration manifested by drug-related hepatic decompensation (eg, encephalopathy etc.) • AST or ALT > 15×ULN • AST/ALT >10.0×ULN lasting > 7 days or associated with clinical symptom • Total bilirubin > 5×ULN (for subjects with increased bilirubin at baseline, total bilirubin > 8×ULN)

Nonhematologic Toxicity (General)	• Grade 4 nonhematologic toxicity (excluding laboratory abnormalities with no clinical significance) • Grade 3 gastrointestinal perforation, thromboembolic event, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, infusion reaction, or wound dehiscence requiring treatment • Grade 3 toxicities lasting >3 days despite optimal supportive therapies (excluding abnormal laboratory values with no clinical significance or controllable hypertension) • Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 within the re-treatment period or requires systemic treatment • Eight or more days of dose interruption of lenvatinib as a result of lenvatinib or nivolumab treatment-related toxicity during Cycle 1*

* For reasons other than toxicity, this will not be considered as a DLT. In this situation, the relevant subject will be excluded from assessments of DLT and new subject will be added. DLT was determined after discussions among the sponsor, the investigator, and the sponsor's responsible medical officer. An efficacy and safety evaluation advisor may be consulted for the consideration as needed.

Part 2
If the dose level is confirmed to be tolerable in Part 1, an additional 20 HCC subjects with no prior systemic therapy will be enrolled. 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.

Number of Subjects

This study will enroll approximately 26 subjects with HCC (6 in Part 1, 20 in Part 2).

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. **Part 1:** HCC for which no other appropriate therapy is available
   Part 2: No prior systemic therapy for advanced/unresectable HCC
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 (Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression to be deemed a target lesion).
   - 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)
   - 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

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. Age ≥20 years at the time of informed consent
13. Life expectancy of 12 weeks or more
14. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.
15. Meet the following criteria.

    (1) If patients have an archival tumor sample, they have to agree to submit it to sponsor.

    (2) (Part 2 only) Patients who agree to submit tumor sample obtained by fresh biopsy prior to the first dose of study drug (excluding patients with archival tumor sample or patients with inaccessible tumors of safety concern)

Exclusion Criteria

1. Imaging findings for HCC corresponding to any of the following (Part 1 only):
   - 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 and regorafenib) or any investigational agent within 28 days prior to the first dose of study drugs.
3. All toxicities related to prior treatments have not resolved to Grade ≤1 (except alopecia and controlled stable cases).
4. 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

5. Prior treatment with lenvatinib, ONO-4538 (MDX-1106 or BMS-936558), any anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell regulation, or cancer vaccine therapy
6. Subjects who have not recovered adequately from any complications from major surgery prior to starting therapy
7. Subjects having ≥2+ proteinuria on urinalysis (subjects with Grade ≤1 confirmed by quantitative assessment will be eligible).
8. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib
9. 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
10. Prolongation of QTc (Fridericia formula) interval to >480 ms
11. 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
12. Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin and factor X inhibitors which do not require INR monitoring is permitted. Antiplatelet agents are prohibited throughout the study.
13. 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.
14. Surgical arterial-portal venous shunt or arterial-venous shunt
15. 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, or carcinoma in situ including early gastric cancer) within the past 36 months
16. Active infection (any infection requiring systemic treatment). Hepatitis B and C [HBV/HCV] allowed (subjects with chronic HBV infection must have HBV DNA < 100 IU/mL and must be on antiviral therapy.)
17. Active co-infection with:
    1)Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV DNA and HCV RNA, OR
    2)Hepatitis D infection in subjects with hepatitis B
18. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.
19. Subjects with any active, known, or suspected autoimmune disease, with the following exceptions:
    1)Subjects with vitiligo, type 1 diabetes mellitus, resolved childhood asthma or atopy are permitted to enroll.
    2)Subjects with suspected autoimmune thyroid disorders may be enrolled if they are currently euthyroid or with residual hypothyroidism requiring only hormone replacement.
    3)Subjects with psoriasis requiring systemic therapy must be excluded from enrollment
20. Any history of interstitial lung disease, and interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity

21. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of study administration. Inhaled or topical steroids and adrenal replacement doses >10 mg/day prednisone equivalents are permitted in the absence of active autoimmune disease.
22. Subjects with meningeal carcinomatosis
23. Subjects with any current brain or subdural metastases
24. Subjects who are known to be positive for Human Immunodeficiency Virus (HIV).
25. History of clinically significant hepatic encephalopathy
26. Serious nonhealing wound, ulcer, or bone fracture
27. 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
28. Subjects being treated with drugs that strongly inhibit or induce CYP3A4 and that may be possibly used during this study.
29. Any medical or other condition which, in the opinion of the investigator or subinvestigator, would preclude participation in a clinical trial
30. 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). 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 (females who discontinued breastfeeding will be eligible).
31. Women of childbearing potential or men of impregnate potential who don't agree that both the subject and her partner will use the following methods of contraception for periods from before informed consent to during the clinical study and 5 months later (for male subjects 30 days) from last administration of study drug. For contraception method, subject must agree to use any 2 of the following methods: vasectomy or condom for a male subject or partner, bilateral tubal ligation, diaphragm, intrauterine device, or use of oral contraception from at least 28 days before starting the study treatment for a female subject or partner.
32. Participants who have received a live/attenuated vaccine within 28 days of first dose of study drugs

Study Treatments

Study drug in the study defines as E7080/lenvatinib and ONO-4538/nivolumab.

Lenvatinib

Lenvatinib is provided as 4-mg capsule. Lenvatinib will be administered once a day (with or without food) in 4-week cycles at approximately the same time each day. On Day 1 and Day 15 of each cycle, in case concomitantly administered, it will be administered immediately after completion of nivolumab administration.

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.

Nivolumab

Nivolumab is a clear to opalescent, colorless to pale-yellow liquid. Nivolumab injection for intravenous infusion is supplied as vials. Nivolumab will be administered as a dose of 240 mg as a 30-minute IV infusion, Q2W.

Study Treatment Dose Modification

1. Cycle 1 (Part 1 only)

a. If DLT occurs:

Relationship to lenvatinib and/or nivolumab will be evaluated, then lenvatinib and/or infusion of nivolumab should be interrupted or discontinued immediately. Treatment may be resumed at same dose level of nivolumab 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) or baseline, when investigator or subinvestigator decides to continue the study.

b. No DLT

Relationship to lenvatinib and/or nivolumab will be evaluated, then lenvatinib and/or nivolumab will be interrupted. Dose adjustments for management of intolerable toxicities will be made according to the guidelines provided in the table below. Lenvatinib and nivolumab should be resumed at the same dose level, and dose reduction is not allowed.

2. Cycle 2 and onward (and applies to Cycle 1 and onward of part 2)

Relationship to lenvatinib and/or nivolumab will be evaluated, then necessity of dose modification (either or both drugs) will be determined. Dose adjustment for management of intolerable toxicities will be made according to the guidelines provided in the table below.

Lenvatinib

Treatment-Related Toxicity[a,b]		Dose Adjustment
Hematologic Toxicities and Proteinuria	Grade 3 [c]	Interrupt until resolved to Grade 0-2 or baseline. In the first occurrence, dose should not be changed. In the second occurrence or later, reduce lenvatinib by 1 dose level.
	Grade 4	Interrupt until resolved to Grade 0-2 or baseline. Reduce lenvatinib by 1 more dose level.
Nonhematologic Toxicities	Intolerable Grade 2[d]	Dose of lenvatinib will be reduced by 1 dose level with or without dose interruption.
	Grade 3[c,e,f]	Interrupt until resolved to Grade 0-1 or baseline. Reduce lenvatinib by 1 dose level.
	Grade 4[f, g]	Discontinue lenvatinib

a: An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) will require discussion with the sponsor before treatment can be resumed. During treatment interruption, repeat AEs assessment about every 7 days (until restarting administration).
b: Initiate optimal medical management for nausea, vomiting, diarrhea, and/or hypothyroidism prior to interruption or dose reduction of lenvatinib.
c: Not applicable to abnormal clinical laboratory values that are not clinically significant based on the judgment of the investigator or subinvestigator.
d: Grade 2 toxicities will be determined to be tolerable or intolerable by both the subject and investigator or subinvestigator.
e: 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.
f: For asymptomatic Grade ≥3 elevations of amylase and lipase, sponsor should be consulted to obtain permission to continue treatment.
g: Excluding laboratory abnormalities judged to be nonlife-threatening, which should be managed as Grade 3.

For management of hypertension, refer to the main protocol text for instructions without applying the table above.

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

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

Nivolumab

Treatment-Related Toxicity[a]	Dose Delay Criteria	Criteria to Resume Dosing
Skin-related adverse event	Grade 3	Grade ≤ 1 or baseline value
Fatigue	Grade 3	Grade ≤2
Laboratory abnormality (except for AST/ALT)	Grade 3 (except for amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis)	Grade ≤ 1 or baseline value (T-Bil: baseline CTCAE Grade or normal)
AST/ALT	Baseline AST/ALT is within normal limits: Grade ≥2. Baseline AST/ALT is Grade 1: Grade ≥3. Baseline AST/ALT is Grade 2: ≥two-fold of baseline value or ≥8x ULN	Baseline CTCAE Grade or normal
Pulmonary toxicity, diarrhea, or colitis	Grade≥2	Baseline
Others	Grade ≥2	Grade ≤ 1 or baseline value (Endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.)

a: A delay of nivolumab for more than 6 weeks will require sponsor's approval before treatment can be resumed.

Discontinuation Criteria of Nivolumab

Nivolumab treatment should be discontinued for the following AEs related to nivolumab:

- Any Grade 2 uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period or requires systemic treatment
- Any Grade 3 uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction
- Any Grade 3 thrombocytopenia lasting >7 days or associated with bleeding
- Any Grade 3 AE lasting >7 days, with the exceptions of skin, laboratory abnormalities, endocrinopathies adequately controlled with only physiologic hormone replacement
- Any hepatotoxicity as below:
  - AST or ALT >10×ULN lasting >2 weeks
  - AST or ALT >15×ULN
  - For subjects with total bilirubin ≤ULN at baseline: total bilirubin > 5×ULN
  - For subjects with increased bilirubin at baseline: total bilirubin > 8×ULN
- Any Grade 4 AE or laboratory abnormality, except for the following
  - Neutropenia <7 days
  - Lymphopenia or leukopenia
  - Amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis

- Isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Endocrinopathy adverse events that are adequately controlled with physiologic hormone replacement

Duration of Treatment

Treatment will be continued until the criteria for discontinuation is met.

Criteria for discontinuation:

1. The subject refuses to continue participation in the study or wishes to withdraw consent.
2. Major violations of inclusion or exclusion criteria in the protocol are found after study enrollment.
3. Subject is unable to continue the study due to an adverse event, in the opinion of the investigator or subinvestigator.
4. The subject becomes pregnant.
5. Progressive disease (when the principal investigator or subinvestigator and sponsor judges clinical benefit of lenvatinib plus nivolumab is maintained, it can be continued).
6. The investigator or subinvestigator determines that discontinuation in the study is appropriate.

Concomitant Drug/Therapy

Prohibited Concomitant Medications/Therapies

Subjects should not receive other antitumor therapies while on study. If a subject receives additional antitumor therapies other than the study drug, 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.

Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) are prohibited during treatment and until 30 days post last dose.

The following medications are prohibited during the study. During DLT evaluation in Part 1, preventive administration or changes in dose or medication should be prohibited until occurrence of a DLT.

- Antiplatelet agents and anticoagulants that require INR monitoring, such as warfarin (treatments that do not require INR monitoring, such as low molecular weight heparin and certain factor X inhibitors are permitted).
- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (see the note below)

  Note: Following corticosteroids are allowed to use during the study.
- Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption)
- Adrenal replacement steroid doses >10 mg daily prednisone equivalent in the absence of active autoimmune disease.
- Immunosuppressive doses of corticosteroids to treat adverse events (> 10 mg daily prednisone equivalent)
- A brief course of corticosteroids (<3 weeks) for prophylaxis (eg, contrast agent allergy) or treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by

contact allergen)

Assessments

Efficacy

All efficacy endpoints will be based on tumor assessments performed by the investigators using mRECIST. If necessary, independent review using mRECIST and RECIST1.1 will be performed (Part 2 only).

Pharmacokinetic

Plasma concentrations of lenvatinib and serum concentrations of nivolumab will be measured.

Immunogenicity

Anti-nivolumab antibody will also be measured.

Pharmacodynamic/Pharmacogenomic

Blood sample

All subjects must provide blood sample for exploratory biomarker analysis.

Tumor sample

Archival tumor tissue must be provided for exploratory biomarker analysis and development of diagnostic product if available (Part 1 and Part 2). If not available, 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 (Part 2 only).

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, electrocardiograms (ECGs); echocardiograms or multigated acquisition (MUGA) scans including left ventricular ejection fraction (LVEF); and ECOG-PS.

Bioanalytical Methods

Validated methods will be used to measure plasma concentration of lenvatinib and serum concentration of nivolumab. In addition, ADA of nivolumab in serum and neutralizing antibody will be detected using validated methods.

Statistical Methods

Study Endpoints

The following endpoints will be defined based on mRECIST (and RECIST 1.1; optional) except for OS.

ORR is defined as the proportion of subjects who have BOR of CR or PR.

DCR is defined as the proportion of subjects who have BOR of CR or PR or SD (duration from C1D1 to SD has to be ≥7 weeks).

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

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) (Part 2 only).

TTP is defined as the time from the first study dose date to the date of first documentation of disease progression (Part 2 only).

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) (Part 2 only).

TTR is defined as the time from the date of first study dose to the date of first documentation of CR or PR. (Part 2 only).

OS is defined as the time from the date of first study dose to the 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 (Part 2 only).

Analysis Sets

DLT Analysis Set will include all subjects (Part 1 only) who have completed Cycle 1 without major protocol deviation with at least 75% of lenvatinib compliance and at least 2 doses of nivolumab 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 will include all subjects who received at least 1 dose of lenvatinib or nivolumab.

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

The Efficacy Analysis Set will include all subjects who received at least 1 dose of lenvatinib and nivolumab.

The Pharmacodynamic and PGx Analysis Set is the group of subjects who received at least 1 dose of lenvatinib and nivolumab and had at least 1 postdose pharmacodynamic or PGx data.

Efficacy Analyses

Efficacy analyses will be conducted by part based on the Efficacy Analysis Set. Tumor assessment will be analyzed based on the investigator's assessment. If needed, the analysis based on independent review will be conducted.

Part 1: BOR will be summarized, and ORR and their corresponding exact 2-sided 95% confidence interval (CI) will be calculated. DCR and CBR will be summarized in a same manner.

Part 2: In addition to the same analysis as above for Part 1, PFS will be summarized and plotted over time by Kaplan-Meier method. TTP, DOR, TTR, and OS will be summarized similarly. 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). A spider plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions.

Pharmacokinetic and/or Pharmacodynamic Analyses

Pharmacokinetic

The primary PK parameters of lenvatinib in the combination will be calculated by noncompartmental analysis using the PK analysis set (Part 1 only). If warranted, additional analyses may be performed. PK data for lenvatinib and nivolumab is planned to be analyzed using nonlinear mixed effects modeling. PK data for lenvatinib and nivolumab may also be used to explore the exposure-response relationships for antitumor activity/efficacy as well as biomarkers and safety, if feasible. The results of these analyses, if performed, will be reported separately.

Immunogenicity

All immunogenicity analyses will be performed using the Safety Analysis Set. The percentage and frequency of expression will be calculated for serum anti-nivolumab antibodies. If anti-nivolumab antibody develops, presence of neutralizing antibody will be summarized using the frequency and percentage.

Pharmacodynamic and Pharmacogenomics

The effect of lenvatinib-nivolumab combination therapy on soluble and/or tissue biomarkers will be summarized using descriptive statistics.

Tolerability/Safety Analyses

All DLT analyses will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated. DLT will also be calculated by type. Safety analyses other than DLTs will be performed on the Safety Analysis Set. All other safety analyses will be performed on the Safety Analysis Set by part. The number and percentage of subjects with treatment-emergent AEs (TEAEs) and treatment-emergent SAEs will be summarized by system organ class (SOC) and preferred term (PT). Safety data will be summarized using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables).

Sample Size Rationale

A sample size of approximately 26 subjects will be enrolled in this study, 6 patients for Part 1 and 20 patients for Part 2. Six subjects in Part 1 was deemed appropriate to evaluate the tolerability of the dose and perform preliminary safety assessment. Twenty subjects in Part 2 was determined to further evaluate the safety and preliminary efficacy. The probability to detect at least 1 development of intolerable treatment-related AEs with a incidence of 10%, 15% or 20% in 20 subjects was 87.8%, 96.1%, or 98.8%, respectively. Therefore, the sample size is determined to be approximately 20 subjects.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AASLD	American Association for the Study of Liver Diseases
AFP	α-fetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-inf)	area under the concentration-time curve from zero time extrapolated to infinite time
AUC(0-t)	area under the concentration-time curve from zero time to time of last quantifiable concentration
BOR	best overall response
BUN	blood urea nitrogen
βhCG	beta human chorionic gonadotropin
CBR	clinical benefit rate
CL	total clearance
C_{avgss}	average steady-state plasma concentration
C_{max}	maximum observed concentration
C_{peak}	concentration at end of infusion
C_{trough}	trough drug concentration at steady-state
CR	complete response
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
C#D#	Cycle# Day#
DNA	deoxyribonucleic acid
DCR	disease control rate
DOR	Duration of response
DLT	dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group

FDA	United States Food and Drug Administration
FFPE	formalin fixed, paraffin-embedded
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
γ-GTP	gamma glutamyl transferase
HBc	hepatitis B virus core
HBs	hepatitis B virus surface
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Council for Harmonization
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition technique
mRECIST	modified Response Evaluation Criteria in Solid Tumor
NE	not evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	Programmed cell death-1
PDGF	platelet derived growth factor
PDGFRα	platelet derived growth factor receptor α
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PR	partial response

PS	performance status
PT	preferred term
QOL	quality of life
QT	QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SOC	system organ class
SOP	standard operating procedure
SPO_2	percutaneous oxygen saturation
$t_{½}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
TEMAV	treatment emergent markedly abnormal laboratory values
t_{max}	time at which the highest drug concentration occurs
TNM	tumor, nodes, metastasis
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
Vss	volume of distribution at steady-state
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) constituted and functioning in accordance with Good Clinical Practice (GCP). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change of telephone numbers). Documentation of IRB compliance with GCP regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB chairman must be sent to the head of the medical institution with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee. If the IRB decides to suspend or terminate the study, the head of the medical institution will immediately send the notice of study suspension or termination by the IRB to the sponsor.

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

5.2 Ethical Conduct of the Study

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

- Principles of the World Medical Association Declaration of Helsinki
- GCP

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator or subinvestigator 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 are read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB-approved ICF must be prepared by the investigator in accordance with GCP and all applicable local regulations in collaboration with the sponsor. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the investigator or subinvestigator (and clinical research coordinator, if needed). The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

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

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsor in Japan (1 site for Part 1, not determined for Part 2).

The name and telephone and fax numbers of the contact personnel at the sponsor are listed in the Attachment.

7 INTRODUCTION

Primary liver cancer is the 6th most common cancer and is the 2nd most common cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancer. The majority of HCC occurs in Asia or Africa, however, the incidence has been rising in a number of low-rate areas including Europe and the United States.

The prognosis for advanced HCC is very poor. Although therapies including arterial infusion and radiation therapy have been tried, none has proven highly successful. Sorafenib is the current standard of therapy for advanced HCC patients following clinical results from the 2 pivotal trials in Western and Asian patients. Regorafenib was approved for the second-line treatment of patients with unresectable hepatocellular carcinoma who have progressed after treatment with cancer chemotherapy.

E7080/lenvatinib was developed at Eisai Tsukuba Research Laboratories. Lenvatinib selectively inhibits VEGF receptors, KDR (VEGFR2), and is being developed as a novel

anticancer therapy through inhibition of angiogenesis. A multinational Phase 3 study in subjects with HCC demonstrated noninferiority of lenvatinib to sorafenib for overall survival (OS).

ONO-4538/nivolumab is a human anti-human programmed death-1 (PD-1, also known as CD279) monoclonal antibody, developed by Ono Pharmaceutical and Medarex (current Bristol-Myers Squibb). Clinical development program of nivolumab is currently underway by Ono Pharmaceutical and Bristol-Myers Squibb. Nivolumab is approved in many countries including the United States, European Union, and Japan. Nivolumab monotherapy has shown clinical benefit in HCC patients who have previously been treated with sorafenib and has been approved for use in the United States and elsewhere. In addition, an international phase 3 study comparing nivolumab and sorafenib in progressed HCC patients who have not been treated with systemic chemotherapy (ONO-4538-35 / CA209459), and an international phase 3 study comparing the combination of nivolumab and ipilimumab with sorafenib or lenvatinib in progressed HCC patients who have not been treated (ONO-4538-92/CA2099DW) is currently ongoing.

Unmet medical needs in the treatment of HCC still exist, and nivolumab is effective across a broad range of tumor types. The current study is designed to evaluate the safety and efficacy of a combination of lenvatinib plus nivolumab in subjects with HCC.

8 STUDY OBJECTIVES

8.1 Primary Objective

- To evaluate the tolerability and safety for combination of lenvatinib plus nivolumab in subjects with hepatocellular carcinoma (HCC)

8.2 Secondary Objectives

- To evaluate the following efficacy endpoints based on investigator review in subjects with HCC:
  - Objective response rate (ORR)
- To assess the pharmacokinetic (PK) profile of lenvatinib and nivolumab

8.3 Exploratory Objective(s)

CCI

[redacted]

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study will be conducted in 2 parts (Part 1 and Part 2). Part 1 will assess the tolerability of lenvatinib in combination with nivolumab in subjects with HCC for which no other appropriate therapy is available. Part 2 is to further characterize the safety and to assess preliminary efficacy of the combination therapy in subjects with HCC with no prior systemic therapy.

9.1.1 Part 1

In Part 1, the tolerability review of Cycle 1 (4 weeks) will be conducted by dose limiting toxicities (DLTs). Study treatment and starting dose are as follows:

Lenvatinib: 12 mg (Body weight [BW] ≥60 kg) or 8 mg (BW <60 kg) once daily orally

Nivolumab: 240 mg (every 2 weeks [Q2W], intravenous [IV]) (Days 1 and 15 of each cycle)

The tolerability will be reviewed based on dose limiting toxicity (DLT) of Cycle 1 (4 weeks) according to the following procedures and criteria.

First, 3 subjects will be enrolled.

7. DLT occurs in 0 or 1 of 3 subjects.
   Add 3 more subjects and assess in a total of 6 subjects.

   1. DLT occurs in 0 or 1 of 6 subjects.
      This dose level is judged to be tolerable.

   2. DLT occurs in 2 or more of 6 subjects.
      The tolerability with this dose level will be discussed by the sponsor, sponsor's responsible medical officer, and investigator.

8. DLT occurs in 2 or more of 3 subjects.
   The tolerability with this dose level and appropriateness of additional enrollment will be discussed by the sponsor, sponsor's responsible medical officer, and investigator.

In this dose level, at least 3 subjects treated with lenvatinib 12 mg (BW ≥60 kg) and nivolumab need to be included in the 6 subjects for DLT evaluation. If this dose level is not tolerable, upon discussions between the sponsor, sponsor's responsible medical officer, and

investigator, the lower dose level of cohort will be considered or the study will be discontinued, and the protocol will be amended as necessary. An efficacy and safety evaluation advisor may be consulted for the consideration as needed.

A DLT is defined as any of the events noted in the table below considered to be at least possibly related to lenvatinib and/or nivolumab occurring during Cycle 1.

Table 1 Dose Limiting Toxicities

Hematologic toxicity	• Febrile neutropenia • Grade 4 neutropenia lasting >7 days • Grade 4 thrombocytopenia • Grade 3 thrombocytopenia lasting >7 days or associated with bleeding • Grade 4 anemia
Nonhematologic Toxicity (Hepatotoxicity)	• Clinical deterioration manifested by drug-related hepatic decompensation (eg, encephalopathy etc.) • AST or ALT > 15×ULN • AST/ALT >10.0×ULN lasting > 7 days or associated with clinical symptom • Total bilirubin > 5×ULN (for subjects with increased bilirubin at baseline, total bilirubin > 8×ULN)
Nonhematologic Toxicity (General)	• Grade 4 nonhematologic toxicity (excluding laboratory abnormalities with no clinical significance) • Grade 3 gastrointestinal perforation, thromboembolic event, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, infusion reaction, or wound dehiscence requiring treatment • Grade 3 toxicities lasting >3 days despite optimal supportive therapies (excluding abnormal laboratory values with no clinical significance or controllable hypertension) • Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 within the re-treatment period or requires systemic treatment • Eight or more days of dose interruption of lenvatinib as a result of lenvatinib or nivolumab treatment-related toxicity during Cycle 1*

* For reasons other than toxicity, this will not be considered as a DLT. In this situation, the relevant subject will be excluded from assessments of DLT and new subject will be added. DLT was determined after discussions among the sponsor, the investigator, and the sponsor's responsible medical officer. An efficacy and safety evaluation advisor may be consulted for the consideration as needed.

9.1.2 Part 2

If the dose level is confirmed to be tolerable in Part 1, an additional 20 HCC subjects with no prior systemic therapy will be enrolled. 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.

9.1.3 Study Design

An overview of the study design is presented in Figure 1. Part 1 and Part 2 will consist of a Pretreatment Phase, a Treatment Phase, and a Follow-up Phase.

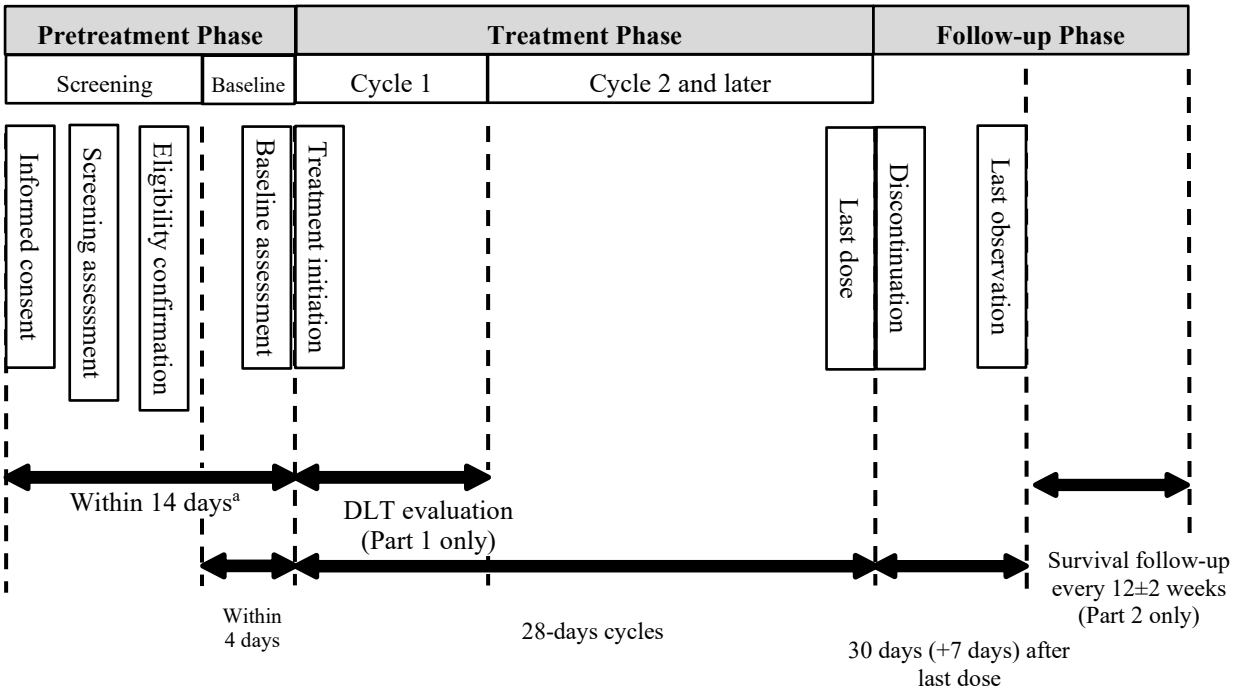


Figure 1 Study Design

DLT = dose limiting toxicity.

a: Screening assessment should be performed within 14 days of first dose. (Informed consent can be obtained within 28 days of first dose.)

9.1.3.1 Pretreatment Phase

The Pretreatment Phase will involve obtaining informed consent, a screening assessment, and a baseline assessment. Screening will occur within 14 days before starting study drug administration after obtaining written informed consent. 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 (informed consent can be obtained within 28 days of first dose). After screening assessments, the sponsor will be informed of eligibility of the patient by the investigator or subinvestigator. The baseline assessment will be conducted within 4 days before starting study drug administration in order to confirm that the patient meet the eligibility requirement before moving to the Treatment Phase.

9.1.3.2 Treatment Phase

In the Treatment Phase, subjects will receive lenvatinib in combination with nivolumab. The Treatment Phase will begin with the first dose of study drug administration on Cycle 1 Day 1. Each cycle is 4 weeks long and subjects will continue treatment until they meet any of the criteria in "Discontinuation Criteria by Subject (see Section 9.3.3.1)".

In Part 1, subjects will be hospitalized during the Cycle 1, however, outpatient is allowed after Cycle 1 Day 15, when the investigator or subinvestigator judges that the subject's safety is ensured.

9.1.3.3 Follow-up Phase

The Follow-up Phase will consist of the examination at study discontinuation and the last observation visit which occurs 30 days after final administration of study drug. The subject who discontinues study will have a discontinuation visit and last observation which occurs 30 days after final administration of study drug. If a new anticancer agent needs to be immediately started due to deterioration in the subject's condition, the final observation visit can be conducted before 30 days after the last dose of the study drug has passed but prior to starting a new anticancer agent. If the last observation visit occurs within 7 days after study drug discontinuation, discontinuation data can be used as the last observation data.

In Part 2, all subjects will be followed for survival until death every 12 weeks (±2 week) from the date of discontinuation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued until discontinuation of the last subject or for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2, whichever occurs later.

9.2 Discussion of Study Design, Including Choice of Control Groups

This is the study to evaluate the tolerability and safety and to explore the efficacy of a combination of lenvatinib plus nivolumab in subjects with HCC. In view of seriousness in targeted subjects and ethical conduct of the study, placebo group will not be employed and open design will be used. This study was designed according to "The Guidelines for Clinical Evaluation of Anti-Cancer Drugs in Japan (Notification No. 1101001 issued on November 1, 2005)."

9.3 Selection of Study Population

Approximately 26 subjects (6 in Part 1, 20 in Part 2) will be enrolled at sites in Japan (1 site for Part 1, TBD for Part 2). Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

1. 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 (Appendix 1), including cirrhosis of any etiology and/or chronic hepatitis B or C infection

2. **Part 1:** HCC for which no other appropriate therapy is available

   Part 2: No prior systemic therapy for advanced/unresectable HCC
3. Subjects categorized to stage B (not applicable for transarterial chemoembolization [TACE]), or stage C based on Barcelona Clinic Liver Cancer (BCLC) staging system (Appendix 3)
4. At least 1 measurable target lesion according to mRECIST meeting the following criteria (Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression to be deemed a target lesion).
   - 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)
   - 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
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. Age ≥20 years at the time of informed consent
13. Life expectancy of 12 weeks or more
14. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol
15. Meet the following criteria

(1) If patients have an archival tumor sample, they have to agree to submit it to sponsor.

(2) (Part 2 only) Patients who agree to submit tumor sample obtained by fresh biopsy prior to the first dose of study drug (excluding patients with archival tumor sample or with inaccessible tumors of safety concern)

9.3.2 Exclusion Criteria

1. Imaging findings for HCC corresponding to any of the following (Part 1 only):
   - 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 and regorafenib) or any investigational agent within 28 days prior to the first dose of study drugs.
3. All toxicities related to prior treatments have not resolved to Grade ≤1 (except alopecia and controlled stable cases).
4. 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
5. Prior treatment with lenvatinib, ONO-4538 (MDX-1106 or BMS-936558), any anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell regulation, or cancer vaccine therapy
6. Subjects who has not recovered adequately from any complications from major surgery prior to starting therapy.
7. Subjects having ≥2+ proteinuria on urinalysis (subjects with Grade ≤1 confirmed by quantitative assessment will be eligible).
8. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.
9. New York Heart Association (Appendix 6) 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.
10. Prolongation of QTc (Fridericia formula) interval to >480 ms
11. 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
12. Bleeding or thrombotic disorders or use of anticoagulants requiring therapeutic INR monitoring, eg, warfarin or similar agents. Treatment with low molecular weight heparin and factor X inhibitors which do not require INR monitoring is permitted. Antiplatelet agents are prohibited throughout the study.
13. 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.
14. Surgical arterial-portal venous shunt or arterial-venous shunt

15. 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, or carcinoma in situ including early gastric cancer) within the past 36 months
16. Active infection (any infection requiring systemic treatment). Hepatitis B and C [HBV/HCV] allowed (subjects with chronic HBV infection must have HBV DNA < 100 IU/mL and must be on antiviral therapy.)
17. Active co-infection with:
    4)Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV DNA and HCV RNA, OR
    5)Hepatitis D infection in subjects with hepatitis B
18. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.
19. Subjects with any active, known, or suspected autoimmune disease, with the following exceptions:
    1)Subjects with vitiligo, type 1 diabetes mellitus, resolved childhood asthma or atopy are permitted to enroll.
    2)Subjects with suspected autoimmune thyroid disorders may be enrolled if they are currently euthyroid or with residual hypothyroidism requiring only hormone replacement.
    3)Subjects with psoriasis requiring systemic therapy must be excluded from enrollment
20. Any history of interstitial lung disease, and interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity
21. Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of study administration. Inhaled or topical steroids and adrenal replacement doses >10 mg/day prednisone equivalents are permitted in the absence of active autoimmune disease.
22. Subjects with meningeal carcinomatosis
23. Subjects with any current brain or subdural metastases
24. Subjects who are known to be positive for Human Immunodeficiency Virus (HIV).
25. History of clinically significant hepatic encephalopathy
26. Serious nonhealing wound, ulcer, or bone fracture
27. 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
28. Subjects being treated with drugs that strongly inhibit or induce CYP3A4 and that may be possibly used during this study.
29. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial
30. 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). 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 (females who discontinued breastfeeding will be eligible)

31. Women of childbearing potential or man of impregnate potential who don't agree that both the subject and her partner will use the following methods of contraception for periods from before informed consent to during the clinical study and 5 months later (for male subjects 30 days) from last administration of study drug. For contraception method, subject must agree to use any 2 of the following methods: vasectomy or condom for a male subject or partner, bilateral tubal ligation, diaphragm, intrauterine device, or use of oral contraception from at least 28 days before starting the study treatment for a female subject or partner.
32. Participants who have received a live/attenuated vaccine within 28 days of first dose of study drugs

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator or subinvestigator 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 complete protocol-specified discontinuation visits and procedures and survival follow-up unless the subject withdraws consent. If a subject withdraws consent, the date will be documented in the source documents.

In Part 2, all subjects will be followed for survival until death every 12 weeks (±2 week) from the date of discontinuation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued until discontinuation of the last subject or for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2, whichever occurs later.

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.

1. The subject refuses to continue participation in the study or wishes to withdraw consent.
2. Major violations of inclusion or exclusion criteria in the protocol are found after study enrollment.
3. Subject is unable to continue the study due to an adverse event, in the opinion of the investigator or subinvestigator.
4. The subject becomes pregnant.
5. Progressive disease (when the investigator or subinvestigator judges clinical benefit of lenvatinib plus nivolumab is maintained, it can be continued).
6. The investigator or subinvestigator determines that discontinuation in the study is appropriate.

9.4 Treatments

For this study, the study drugs are E7080/lenvatinib and ONO-4538/nivolumab.

9.4.1 Treatments Administered

9.4.1.1 Lenvatinib

Lenvatinib is provided as 4-mg capsule. Lenvatinib will be administered once a day (with or without food) in 4-week cycles at approximately the same time each day. On Day 1 and Day 15 of each cycle, in case concomitantly administered, it will be administered immediately after completion of nivolumab administration.

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.

9.4.1.2 Nivolumab

Nivolumab injection for intravenous infusion contains 100 mg/10 mL of nivolumab in each vial. Nivolumab will be administered at a dose of 240 mg as an IV infusion over 30 minutes, Q2W (Day 1 and Day 15 of each cycle). Please refer to the current version of the Investigator's Brochure (IB) and instructions for handling of investigational products for complete storage, preparation and administration information for nivolumab.

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

9.4.1.3.1 CYCLE 1 (PART 1 ONLY)

1. If DLT occurs:

Relationship of the DLT to lenvatinib and/or nivolumab will be evaluated, then lenvatinib and/or infusion of nivolumab should be interrupted or discontinued immediately. Treatment may be resumed at the same dose level of nivolumab 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) or baseline, when investigator or subinvestigator decides to continue the study.

2. No DLT occurs:

Relationship of the DLT to lenvatinib and/or nivolumab will be evaluated, then lenvatinib and/or nivolumab will be interrupted. Dose adjustments for management of intolerable toxicities will be made according to the guidelines provided in the table below. Lenvatinib and nivolumab should be resumed at the same dose level, and dose reduction is not allowed.

9.4.1.3.2 CYCLE 2 AND ONWARD (AND APPLIES TO CYCLE 1 AND ONWARD OF PART 2)

Relationship to lenvatinib and/or nivolumab will be evaluated, then necessity of dose modification (either or both drugs) will be determined. Dose adjustments for management of intolerable toxicities will be made according to the guidelines provided in the table below.

9.4.1.3.2.1 Criteria for Interruption of Treatment, Dose Reduction, and Discontinuation of Lenvatinib

Dose adjustments for management of intolerable toxicities will be made according to the guidelines shown in Table 2. Lenvatinib dose should be reduced as shown in Table 3. For management of hypertension, refer to Section 9.4.1.4 without consulting the table below.

Table 2 Dose Adjustments of Lenvatinib

Treatment-Related Toxicity [a,b]		Dose Adjustment
Hematologic Toxicities and Proteinuria	Grade 3 [c]	Interrupt until resolved to Grade 0-2 or baseline. In the first occurrence, dose should not be changed. In the second occurrence or later, reduce lenvatinib by 1 dose level.
	Grade 4	Interrupt until resolved to Grade 0-2 or baseline. Reduce lenvatinib by 1 more dose level.
Nonhematologic Toxicities	Intolerable Grade 2[d]	Dose of lenvatinib will be reduced by 1 dose level with or without dose interruption.
	Grade 3[c,e,f]	Interrupt until resolved to Grade 0-1 or baseline. Reduce lenvatinib by 1 dose level.
	Grade 4 [f, g]	Discontinue lenvatinib

a: An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) will require discussion with the sponsor before treatment can be resumed. During treatment interruption, repeat AEs assessment about every 7 days (until restarting administration).
b: Initiate optimal medical management for nausea, vomiting, diarrhea, and/or hypothyroidism prior to interruption or dose reduction of lenvatinib.
c: Not applicable to abnormal clinical laboratory values that are not clinically significant based on the judgment of the investigator or subinvestigator.
d: Grade 2 toxicities will be determined to be tolerable or intolerable by both the subject and investigator or subinvestigator.
e: 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.
f: For asymptomatic Grade ≥3 elevations of amylase and lipase, sponsor should be consulted to obtain permission to continue treatment.
g: Excluding laboratory abnormalities judged to be nonlife-threatening, which should be managed as Grade 3.

Table 3 Dose Reduction Recommendations for Lenvatinib

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

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

9.4.1.3.2.2 Criteria for Delay of Treatment, Resumption, and Discontinuation of Nivolumab

9.4.1.3.2.2.1 Criteria for Delay of Treatment and Resumption of Nivolumab

Dose adjustments for management of intolerable toxicities will be made according to the guidelines shown in Table 4.

Table 4 Dose Delay and Resuming Dosing of Nivolumab

Treatment-Related Toxicity[a]	Dose Delay Criteria	Criteria to Resume Dosing
Skin-related adverse event	Grade 3	Grade ≤ 1 or baseline value
Fatigue	Grade 3	Grade ≤2
Laboratory abnormality (except for AST/ALT)	Grade 3 (except for amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis)	Grade ≤ 1 or baseline value (T-Bil: baseline CTCAE Grade or normal)
AST/ALT	Baseline AST/ALT is within normal limits: Grade ≥2. Baseline AST/ALT is Grade 1: Grade ≥3. Baseline AST/ALT is Grade 2: ≥two-fold of baseline value or ≥8x ULN	Baseline CTCAE Grade or normal
Pulmonary toxicity, diarrhea, or colitis	Grade≥2	Baseline
Others	Grade ≥2	Grade ≤ 1 or baseline value (Endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.)

ULN: upper limit of normal.
a: A delay of nivolumab for more than 6 weeks will require sponsor's approval before treatment can be resumed.

9.4.1.3.2.2.2 Discontinuation Criteria of Nivolumab

Nivolumab treatment should be discontinued for the following AEs related to nivolumab:

- Any Grade 2 uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period or requires systemic treatment.
- Any Grade 3 uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction.
- Any Grade 3 thrombocytopenia lasting >7 days or associated with bleeding.
- Any Grade 3 AE lasting >7 days, with the exceptions of skin, laboratory abnormalities, endocrinopathies adequately controlled with only physiologic hormone replacement.
- Any hepatotoxicity as below:

  - AST or ALT >10×ULN for >2 weeks
  - AST or ALT >15×ULN
  - For subjects with total bilirubin ≤ULN at baseline: total bilirubin >5×ULN
  - For subjects with increased bilirubin at baseline: total bilirubin >8×ULN
- Any Grade 4 AE or laboratory abnormality, except for the following
  - Neutropenia <7 days
  - Lymphopenia or leukopenia
  - Amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
  - Isolated electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Endocrinopathy adverse events that are adequately controlled with physiologic hormone replacement.

9.4.1.4 Management of Hypertension

Guidelines for assessment and management of hypertension are summarized as follows. CTCAE v4.03 grading for hypertension will be based on BP measurements only (and not on the number of antihypertensive medications).

1. When blood pressure (BP) is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), BP measurement should be repeated at least 5 min apart. In this case, BP assessment is defined as the mean value of two measurements at least 5 minutes apart.
2. When systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is observed in the 1st BP assessment, the 2nd BP assessment should be repeated at least 30 min apart. The 2nd BP assessment is defined as the mean value of two measurements at least 5 minutes apart. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is firstly observed on the 2nd BP assessment. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensives should be added.
3. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg continues despite optimal management of hypertension, lenvatinib should be interrupted and resumed according to Table 3 at a dose of one-dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
4. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs despite the optimal management of hypertension, one-dose level reduction should be attempted.
5. Discontinue lenvatinib administration when Grade 4 hypertension (life-threatening) is present.

9.4.1.5 Management of Proteinuria

Guidelines for assessment and management of proteinuria are summarized as follows.

- Initial episode of proteinuria: if proteinuria ≥2+ is detected on urinalysis, lenvatinib and nivolumab will be continued and a 24-hour urine collection for total protein or a spot urine protein/creatinine ratio will be obtained as soon as possible to verify the grade of proteinuria. Grading according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE v4.03) will be based on the 24-hour urinary protein result or urine protein/creatinine ratio. Management of lenvatinib administration will be based on the grade of proteinuria according to the Dose Adjustment provided in Table 2.
- Recurrence or deterioration of proteinuria: if proteinuria 3+ or 4+ on urine dipstick is detected, lenvatinib and nivolumab will be continued and a 24-hour urine collection for total protein or a spot urine protein/creatinine ratio will be obtained as soon as possible to verify the grade of proteinuria. Management of study drug administration will be based on the grade of proteinuria according to the Dose Adjustment provided in Table 2.
- If an event of proteinuria ≥2 occurs, the subject must undergo urine dipstick testing (on Day 15 or more frequently if clinically indicated) until results are 1+ or negative for 3 consecutive months.

9.4.1.6 Management Algorithms for Immuno-Oncology Agents

The following groups of AEs will be managed by "Appendix 3 Management Algorithms" found in the current nivolumab IB:

- Gastrointestinal
- Renal
- Pulmonary
- Endocrinopathy
- Skin
- Neurological

Please note that management algorithms of this protocol for the hepatic AEs are changed as below:

- If AST or ALT elevation does not improve in 3 to 5 days of dose delay or worsen, methylprednisolone 0.5 to 2 mg/kg or oral steroids equivalent will start.
- If AST or ALT >8×ULN occurs, methylprednisolone 1 to 2 mg/kg or oral steroids equivalent will start immediately.
- Subjects who started steroids should be consulted with the sponsor within 24 hours of corticosteroids initiation. Consultation with gastroenterologist will be recommended.
- If AST or ALT elevation does not improve in 3 to 5 days or worsen, addition of mycophenolate mofetil 1 g twice daily should be considered with the sponsor.

- If AST or ALT elevation returns to 1 grade below, steroids can be tapered over at least 1 month.

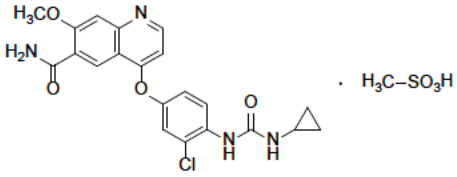
As shown in Section 9.4.1.3.2.2.1, if AST or ALT elevation returns to baseline and a subject does not meet nivolumab discontinuation criteria (Section 9.4.1.3.2.2.2), nivolumab can be resumed.

9.4.2 Identity of Investigational Products

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

Lenvatinib is provided as 4-mg capsule. Nivolumab injection for intravenous infusion is provided as vials. Nivolumab is a clear to opalescent, colorless to pale-yellow liquid. Each vial contains 100 mg/10 mL of nivolumab.

9.4.2.1 Chemical Name, Structural Formula of Lenvatinib

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

9.4.2.2 Chemical Name, Structural Formula of Nivolumab

Nivolumab is a fully human, IgG4 isotype monoclonal antibody that binds anti-human PD-1 and disrupts engagement of the receptor with its ligands PD-L1 and PD-L2.

- Test drug code: ONO-4538
- Generic name: Nivolumab (gene recombination)
- Molecular formula: $C_{6362}H_{9836}N_{1712}O_{1998}S_{42}$ (four polypeptide chains)
  Heavy chain: $C_{2154}H_{3326}N_{576}O_{665}S_{16}$
  Light chain: $C_{1027}H_{1596}N_{280}O_{334}S_5$
- Molecular weight: 143,619.17

9.4.2.3 Comparator Drug

Not applicable.

9.4.2.4 Labeling for Study Drug

The following information is provided on the study drug labeling. Details on labeling and package are shown in the Attachment.

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

9.4.2.5 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. The assigned pharmacist or designee is responsible for ensuring that the study drug is maintained within an established temperature range. The head of the medical institution is responsible for ensuring that records are maintained and the temperature should be monitored continuously by using either an in-house 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 nivolumab. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

The starting dose of lenvatinib is selected as 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg). This dose setting was used in the Phase 3 study of lenvatinib monotherapy versus sorafenib in subjects with unresectable HCC (E7080-G000-304 [Study 304]). This 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). Based on the results of Phase 1, the recommended dose for Phase 2 was determined to be 12 mg QD for HCC subjects with Child-Pugh class A (score 5–6). Most toxicities were manageable by dose interruption and dose reduction, however, majority of subjects with higher lenvatinib exposure or a low body weight required a dose reduction. Subsequently, population pharmacokinetic (PPK) analyses were performed to further explore the starting dose. In order to reduce the number of dose reductions and withdrawals due to AEs, 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). Study 304 demonstrated the noninferiority of lenvatinib to sorafenib in these starting doses setting.

The dose of nivolumab is selected as 240 mg administered as an intravenous (IV) infusion every 2 weeks. In a multiple-dose Phase 1 study of nivolumab conducted overseas (Study CA209003), nivolumab IV at doses from 0.1 to 10 mg/kg was administered every 2 weeks in subjects with malignant tumors. A total of 306 subjects with tumor types including mainly non-small cell lung cancer (NSCLC), malignant melanoma, and renal cell carcinoma (RCC) were enrolled into this study and ONO-4538 demonstrated high antitumor activity at 3 mg/kg or higher. With regard to safety, Phase 1 studies in and outside Japan showed ONO-4538 IV every 2 weeks was well tolerated at doses up to 20 mg/kg in Japan and 10 mg/kg outside Japan (ONO-4538-01 and CA209003).

Based on these efficacy and safety data, ONO-4538 3 mg/kg IV every 2 weeks is being studied in clinical studies in subjects with multiple tumor types. Recently, the use of flat dosing of ONO-4538, without body-weight normalizing, is being investigated to improve ease of administration. Clinical studies in subjects with multiple tumor types are ongoing at a flat dose of 240 mg every 2 weeks and 480 mg every 4 weeks.

To optimize dosing, PPK analyses were performed. ONO-4538 demonstrated linear pharmacokinetics, with a dose-proportional increase in exposure across a dose range of 0.1 mg/kg to 10 mg/kg and no differences were found across tumor types. While both the ONO-4538 clearance and the volume of distribution increased with body weight, the magnitude of the increase was smaller than that of body weight. A previously developed PPK model using data from subjects with NSCLC was further used for 1544 subjects from the 7 studies for malignant melanoma, NSCLC, and RCC. Since the median body weight among these population dataset was 77 kg (range: 35, 160 kg), a flat dose of 240 mg every 2 weeks, the corresponding dose to the 3 mg/kg dose at the body weight of 80 kg, was selected. A PPK model-based simulation was conducted to predict the exposure of ONO-4538 administered 240 mg every 2 weeks. The simulation result was evaluated by comparing simulated exposures at ONO-4538 3 mg/kg and ONO-4538 240 mg every 2 weeks. The data used for simulation were based on randomly selected 1000 subjects from above cancer subjects for each dose setting. No differences have been found in pharmacokinetics across ethnicity and tumor types, suggesting these results based on subjects with malignant melanoma, NSCLC, and RCC could be extrapolated to other tumor types. The time-averaged steady-state concentration (C_{avgss}) produced by 240 mg administered every 2 weeks was expected to be similar to that produced by 3 mg/kg every 2 week at the representative body weight of 80 kg.

ONO-4538 is safe and well tolerated at doses up to 10 mg/kg every 2 weeks. The relationship of exposure and response seems to be flat at doses of 3 mg/kg or more. Based on the above pharmacokinetic, safety, and efficacy analysis data, the safety and efficacy profile of nivolumab 240 mg every 2 weeks was comparable to 3 mg/kg every 2 weeks. Nivolumab is a human monoclonal antibody; possibility of drug-concomitant chemotherapy interactions is extremely low. Based on the above reasons, the flat dose of 240 mg IV every 2 weeks was chosen for this study.

9.4.5 Selection and Timing of Dose for Each Subject

The selection and timing of the lenvatinib and nivolumab for each subject are provided in Section 9.4.1. Lenvatinib will be administered in a fasting state or after a meal. The food effect study of lenvatinib indicated that lenvatinib exposure is not significantly affected by food intake.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent and until 30 days after the final dose of study drug or until the subject initiates new anticancer therapy, whichever is earlier) will be recorded on the CRF. For all drugs, the name, treatment start dates (or timing of starting treatment), treatment end dates, and reason for use will be recorded on the CRF. Concomitant drugs such as premedication, diagnostic agents, solutions, or fluid transfusions provided for surgery, medical examinations, or administrations will be excepted. For concomitant therapy, the name, treatment start dates (or timing of starting treatment), treatment end dates, and reason for use will be recorded on the CRF. Prior therapies on HCC are provided in Section 9.5.1.2.2.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including G-CSF, blood products, blood transfusions, fluid transfusions, antibiotics, steroids, antidiarrheal drugs, or tranquilizers) may be given at the discretion of the investigator or subinvestigator but these therapies or drugs should be used in caution.

9.4.7.1 Drug-Drug Interactions

Lenvatinib's weak in vitro inhibitory and induction potential on cytochrome P450 (CYP) enzymes suggests a low risk of lenvatinib interference with the PK of other drugs metabolized by CYP enzymes. Nonclinical studies identify CYP3A as an important enzyme responsible for human hepatic metabolism of lenvatinib. However, drug-drug interaction clinical studies conducted to test these findings showed that co-administration of lenvatinib with CYP3A/P-glycoprotein (P-gp) inhibitors or inducers is not of clinical concern. Nivolumab is a human monoclonal antibody; possibility of drug-concomitant chemotherapy interactions is extremely low. Also, pharmacokinetic interactions of nivolumab with lenvatinib are not expected because nivolumab has low possibility to affect CYP expression indirectly via cytokine.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

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.

Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) are prohibited during treatment and until 30 days post last dose.

The following medications are prohibited during the study. During DLT evaluation in Part 1, preventive administration or changes in dose or medication should be prohibited until occurrence of a DLT.

- Antiplatelet agents and anticoagulants that require INR monitoring, such as warfarin (treatments that do not require INR monitoring, such as low molecular weight heparin and certain factor X inhibitors are permitted).
- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent.

  Note: Following corticosteroids are allowed to use during the study.
- Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption)
- Adrenal replacement steroid doses >10 mg daily prednisone equivalent in the absence of active autoimmune disease.
- Immunosuppressive doses of corticosteroids to treat adverse events (> 10 mg daily prednisone equivalent)
- A brief course of corticosteroids (<3 weeks) for prophylaxis (e.g., contrast dye allergy) or treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen)

9.4.8 Treatment Compliance

The investigator or subinvestigator will record the treatment compliance. The CRA will review the treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

The assigned pharmacist (or the 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 or subinvestigator 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 assigned pharmacist (or the designee) must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs the subject, unused study drugs that are returned by the subjects (unused study drug-1), unused study drugs that are shipped to site but not dispensed to subjects (unused study drug-2), and return of reconciled study drugs to the sponsor or (a sum of unused study drugs 1 and 2). This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs

dispensing/return reconciliation log, (c) study drugs accountability log, (d) documentation of returns to the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a CRA or a representative of a health authority. Upon completion of unused drug accountability procedures and documentation of study drugs return by the assigned pharmacist (or designee), all unused study drugs are to be returned to the sponsor. Unused study drugs that are returned from the site are hand-delivered to CRAs and to be returned to the sponsor's designated depot.

Drug accountability will be reviewed by the CRA during site visits and at the completion of the study, and throughout 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 Subject ID Number, date of informed consent, age, sex, and race/ethnicity.

9.5.1.2 Pretreatment Assessments

9.5.1.2.1 Medical History and Current medical conditions

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical history that is considered to have effects on safety, efficacy, or PK by the investigator or subinvestigator and medical conditions that are identified at Screening must be noted on the CRF. NYHA Cardiac Disease Classification will be reported on the CRF.

9.5.1.2.2 Primary disease and Prior therapies for primary disease

The following information on primary disease and its prior therapies will be collected at Screening and noted on the CRF.

1. Cause of HCC (hepatitis B, C, alcohol, other, unknown)
2. BCLC staging (Appendix 3)
3. Specify whether disease is confined to liver or metastatic, and if metastatic, to which organs.
4. Detailed medical history of HCC, pathology, if available, Date of diagnosis, TNM staging (Appendix 7)
5. Child-Pugh category (Appendix 4)
6. Prior therapies for primary disease
   - Any surgical procedures
   - Systemic anticancer therapy

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

9.5.1.2.3 GASTROENTEROLOGICAL ENDOSCOPY

Gastroenterological endoscopy will be performed at Screening only. Data within 3 months before the first dose can be used (data before obtaining informed consent can be used).

9.5.1.3 Efficacy Assessments

9.5.1.3.1 TUMOR ASSESSMENTS

All efficacy endpoints will be based on tumor assessments performed by the investigators using mRECIST (Appendix 2). If necessary, independent review using mRECIST and RECIST1.1 will be performed (Part 2 only).

Tumor assessments will be carried out at Screening and then every 8 weeks (Day 1 [±7 days] in odd number cycle) from Day 1 of Cycle 1, or more frequently if disease progression is clinically indicated. 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 can 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. CT or MRI will be performed using contrast media unless there is an allergy to contrast media. If there is known allergy to contrast media, non-contrast CT or MRI will be used.

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, 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, tumor assessments of the chest, abdomen, pelvis, and other areas of known disease at Screening plus newly suspected disease should be performed every 8 weeks (Day 1 [±7 days] in odd number cycle) or more frequently, 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 discontinuation visit is only necessary if more than 4 weeks have passed since the

previous assessment (window for these assessments is within 1 week of discontinuation visit).

9.5.1.3.2 TUMOR MARKER

The investigator or subinvestigator will measure α-fetoprotein (AFP) level. Tumor marker will be tested at Screening and every 8 weeks (Day 1 [±7 days] in odd number cycle), or more frequently if clinically indicated. Tumor marker will be measured at the same time point as tumor assessments. If the data within 28 days prior to dosing are available (data before informed consent can be used).

9.5.1.3.3 SURVIVAL FOLLOW-UP

Subjects will be followed for survival until death every 12 weeks (±2 weeks) from the date of last observation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued until discontinuation of the last subject or for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2, whichever occurs later.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

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

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Table 5 and Table 6 present the detailed blood sampling schedule for pharmacokinetic assessments. Lenvatinib in plasma and nivolumab in serum will be quantified using a validated method. See the Laboratory Manual for a description of collection, handling, and shipping procedures for samples.

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 the day and the day before of pharmacokinetic assessments will be recorded in the CRF. The actual start/stop time of infusion, date, and dose of nivolumab administered will be recorded in the CRF.

Table 5 Blood Sampling Schedule for Pharmacokinetic Assessment of Lenvatinib

Day (Part 1)	Sampling Time	Allowance (as a Target)
Cycle 1 Day 1	Predose of nivolumab	Within –60 minutes before dosing
	1 hour postdose of lenvatinib	±15 minutes
	2 hours postdose of lenvatinib	±15 minutes
	4 hours postdose of lenvatinib	±15 minutes
	8 hours postdose of lenvatinib	±60 minutes
Cycle 1 Day 2	Predose of lenvatinib (24 hours postdose)	Within –60 minutes before dosing
Cycle 1 Day 15	Predose of lenvatinib	Within –60 minutes before dosing

	1 hour postdose of lenvatinib	±15 minutes
	2 hours postdose of lenvatinib	±15 minutes
	4 hours postdose of lenvatinib	±15 minutes
	8 hours postdose of lenvatinib	±60 minutes
Cycle 1 Day 16	Predose of lenvatinib (24 hours postdose)	Within –60 minutes before dosing
Thereafter Day 1 of every Cycle [a]	Predose of lenvatinib	–

a: Blood collection is not required after the 24th cycle [Added in Version 7]

Day (Part 2)	Sampling Time	Allowance (as a Target)
Cycle 1 Day 1	0.5 – 4 hour postdose of lenvatinib	–
Cycle 1 Day 15	Predose of lenvatinib	–
	0.5 – 4 hour postdose of lenvatinib	–
Day 1 of Cycles 2, 4, 6	Predose of lenvatinib	–

Table 6 Blood Sampling Schedule for Pharmacokinetic Assessment of Nivolumab

Day	Sampling Time	Allowance (as a Target)
Cycle 1 Day 1	Predose of nivolumab	Within –60 minutes before dosing
	Just before completion of nivolumab administration	Within –2 minutes before dosing
Cycle 1 Day 15	Predose of nivolumab	Within –60 minutes before dosing
Cycle 2 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 3 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 4 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 5 Day 1	Predose of nivolumab	Within –60 minutes before dosing
	Just before completion of nivolumab administration	Within –5 minutes before dosing
Cycle 5 Day 15	Predose of nivolumab	Within –60 minutes before dosing
Cycle 9 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 13 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Thereafter Day 1 of every 4 cycles	Predose of nivolumab	Within –60 minutes before dosing

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Blood samples, archived tumor tissue samples, and fresh tumor tissue by biopsy will be collected for pharmacodynamic and pharmacogenomic assessment. PD-1 and other relevant biomarkers identified by the new perception or progress of science will be assessed, if needed. Biomarker discovery will be performed to identify pharmacological effect and to predict subject response to lenvatinib and nivolumab as well as for potential use in diagnostic development.

9.5.1.4.2.1 Blood Biomarker

Blood samples for the development of exploratory biomarkers will be collected from all consented subjects at designated time points as specified in the Schedule of Procedures/Assessments (Table 9) (blood samples for nivolumab will be collected in Part 2 only). Instructions for the processing, storage, and shipping of samples will be provided separately in the Laboratory Manual.

9.5.1.4.2.2 Tissue Biomarker

Archival tumor tissue must be provided for biomarker analysis as well as for potential use in diagnostic development if available (Part 1 and Part 2).

In Part 2, if archival tumor tissue is not available, a newly obtained tumor tissue by fresh biopsy must be available prior to the first dose of study drug for biomarker analysis (fresh biopsy is not mandatory for the subject with previous tumor tissue or with inaccessible tumors of safety concern). Instructions for the processing, storage, and shipping of samples will be provided separately in the Laboratory Manual.

Security of the samples, use of the samples, retention of the samples, and subject privacy are provided below.

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

Sample processing, for example DNA 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. At the end of the storage period, samples will be destroyed. Samples may be stored longer if a Heath Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, samples will be stored until the questions have been adequately addressed.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, the sponsor 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 the results of the research project.

Subject Privacy and Disclosure of Data

Samples will be single coded (Subject ID number). No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample.

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. 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:

- Medical institutions
- 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 the clinical study report or a separate 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.

9.5.1.4.3 ANTI-NIVOLUMAB ANTIBODIES

Table 7 presents the detailed blood sampling schedule for anti-nivolumab antibodies. Anti-nivolumab antibodies will be quantified using a validated method. If an anti-nivolumab antibody develops, presence of neutralizing antibody will be detected. See the Laboratory Manual for a description of collection, handling, and shipping procedures for samples.

Table 7 Blood Sampling Schedule for Anti-nivolumab Antibodies

Day	Sampling Time	Allowance (As a Target)
Cycle 1 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 1 Day 15	Predose of nivolumab	Within –60 minutes before dosing
Cycle 2 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 3 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 5 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 9 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Cycle 13 Day 1	Predose of nivolumab	Within –60 minutes before dosing
Thereafter Day 1 of every 4 cycles	Predose of nivolumab	Within –60 minutes before dosing

9.5.1.5 Safety Assessments

Safety assessments include monitoring and recording all AEs, including all grading of CTCAE v4.03, and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; physical examinations; periodic measurement of vital signs; ECGs; and echocardiograms/MUGA scans to assess LVEF.

9.5.1.5.1 ADVERSE EVENTS

An AE is any untoward medical occurrence in a subject. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drugs are lenvatinib and nivolumab.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease found after the time of informed consent, 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, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the 30 days after the last dose or until the subject initiates new anticancer therapy, whichever is earlier. SAEs will also be collected for 30 days after the last dose or until the subject initiates new anticancer therapy, whichever is earlier.

Any laboratory abnormality considered to constitute an AE should be reported on the 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.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF 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 until 30 days after the 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 or subinvestigator 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 v 4.03. 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

An SAE is any untoward medical occurrence that at any dose:

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

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

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error (see Section 9.5.4.2 and 9.5.4.3). These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" 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 at each site.

Table 8 Clinical Laboratory Tests

Category	Parameters
Hematology	RBC count, hemoglobin, hematocrit, platelets, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Anticoagulant test	INR[a]
Chemistry	
Liver function tests	Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, total bilirubin, direct bilirubin
Renal function tests	Blood urea nitrogen, creatinine
Other	Glucose, albumin, total cholesterol, triglycerides, phosphorus, lactate dehydrogenase, total protein, sodium, potassium, chloride, calcium, magnesium, ammonia[b], amylase[c], lipase[c] , ACTH[e], cortisol[e]
Tumor marker	AFP
Thyroid function tests	TSH, FT4
Virus tests[b]	HIV antibody, HCV antibody, HBs antigen, HBs antibody, HBc antibody, HBV DNA, HCV RNA, HDV antibody or HDV RNA[d]
Urinalysis	pH, protein, glucose, ketones, RBCs, specific gravity

AFP = α-fetoprotein, INR = International Normalized Ratio

a: INR will be assessed on C2D1 and every cycle thereafter.

b: Screening only. Data within 28 days before the first dose can be used.

c: Amylase and lipase will be measured at Screening, C2D1 and every cycle thereafter.

d: Subjects with hepatitis B only

e: If necessary, appropriate laboratory tests such as adrenal cortical function test (ACTH, cortisol) to be added.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the CRF. If AEs were assessed during unscheduled visits, all the data corresponding to the laboratory abnormality will also 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], body temperature [in centigrade]), and weight (kg) and percutaneous oxygen saturation (SPO_2) 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 sitting after the subject has been resting. All BP measurements should be performed on the same arm, preferably by the same person.

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). 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 CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 9). 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 may also be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

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

9.5.1.5.7 ECHOCARDIOGRAM OR MULTIPLE GATED ACQUISITION SCAN

An echocardiogram or a MUGA scan (using technetium-99m-pertechnetate) to assess LVEF will be performed at Screening and at discontinuation visit. Echocardiograms or MUGA scans should be performed locally in accordance with the institution's standard practice. Either an echocardiogram or a MUGA scan which 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.

9.5.1.5.8 ECOG PS

An ECOG performance status should be done at each visit as designated in the Schedule of Procedures/Assessments (Table 9).

9.5.1.5.9 OTHER SAFETY ASSESSMENTS

9.5.1.5.9.1 Pregnancy Test

An hCG or β-hCG test will be performed for women of childbearing potential. A serum or urine sample will be taken at visits as designated in the Schedule of Procedures/Assessments (Table 9).

All females will be considered to be of childbearing potential except:

- Females who are postmenopausal (amenorrheic for at least 12 consecutive months without other known or suspected cause)
- Females who have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

- Females who have no possibility to be pregnant due to medical reasons

9.5.1.5.9.2 Viral Tests

Hepatitis B surface (HBs) antigen, HBs antibody, hepatitis B virus core (HBc) antibody, hepatitis C virus (HCV) antibody, HBV-DNA, HCV-RNA, HDV antibody or HDV RNA (hepatitis B only), and HIV antibody tests will be performed at Screening. Data within 28 days before the first dose can be used.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 9 presents the schedule of procedures/assessments for the study.

Table 9 Schedule of Procedures/Assessments in Study E7080-J081-117 (for Part 1 and Part 2)

Phase	Pretreatment		Treatment								Follow-up	
Period	Screening	Baseline[h]	Cycle 1				Cycle 2 or later				Discontinuation	Last observation visit [q]
Day	-14 to -4	-3 to -1	1	8 (±2)	15 (±2)	22 (±2)	1 [l] (±3)	8 [m] (±3)	15 (±3)	22 [m] (±3)	(+7)	30 days after last administration (+7)
Informed consent [a]	X											
Inclusion/exclusion	X	X										
Demographic	X											
Prior medications and complication	X											
ECOG-PS	X	X					X				X [o]	
Physical examination, Vital signs, SPO_2, Height [b], Weight	X	X		X	X	X	X	X	X	X	X [o]	X
12-lead ECG	X	X			X		X				X [o]	
MUGA or echocardiogram	X										X [o]	
Gastroenterological endoscopy	X[f]											
Laboratory test[c]	X	X		X	X	X	X	X	X	X	X [o]	X
Pregnancy test	X	X									X [o]	
Child-Pugh score	X	X					X				X [o]	
Lenvatinib administration			Throughout									
Lenvatinib PK blood sampling			X [i]		X [i]		X [i]					
Nivolumab administration			X		X		X		X			
Nivolumab PK blood sampling			X[s]		X[n]		X[t]		X[u]		X	X
Anti-nivolumab antibodies (ADA) blood samples			X[n]		X[n]		X[v]				X	X
Lenvatinib PD biomarker blood sampling			X[n]		X[n]		X[n]					
Nivolumab PD biomarker blood sampling			X [w]				X [w]				X [w]	
Archival tissues [d]	X											
Biopsy [e]	X											
CT assessment/Tumor marker	X[g]		X [j]								X [p]	
Hospitalization			X [k]									
Survival												X [r]
Adverse event	Throughout											

Table 9 Schedule of Procedures/Assessments in Study E7080-J081-117 (for Part 1 and Part 2)

Concomitant medications/therapies	Throughout

C#D# = Cycle#/Day#, ECOG-PS = Eastern Cooperative Oncology Group performance status, INR= international normalized ratio, MUGA= multiple gated acquisition scan.

a: Screening assessment should be initiated after obtaining informed consent (Informed consent can be obtained within 28 days of first dose).
b: Height (Screening only)
c: Virus test (Screening only, Data within 28 days before the first dose can be used), Ammonia test (Screening only), Hematology, blood chemistry, urinalysis, blood coagulation tests, thyroid function test. If necessary, appropriate laboratory tests such as adrenal cortical function test (ACTH, cortisol) to be added.
d: Effort should be made to obtain during study. Exclude subjects without available archival tissues.
e: Only in Part 2. Exclude subjects with inaccessible tumors for biopsy of safety concern.
f: Data within 3 months before the first dose can be used (data before obtaining informed consent can also be used).
g: Data within 28 days before the first dose can be used (data before obtaining informed consent can also be used).
h: Regarding tests which are performed in both screening and baseline, if screening test is done 4 days before first dose, baseline tests are not required.
i: For Part 1, blood collection at predose, 1, 2, 4, 8, 24 hours postdose of Cycle 1 Day1 and Day 15, and predose of Day 1 of every cycle thereafter. However, blood collection is not required after Cycle 24. For Part 2, blood collection at 0.5 - 4 hours postdose of Cycle1 Day1, pre and 0.5 - 4 hours postdose of Cycle1 Day15 and predose of Cycles 2, 4, 6
j: CT assessments (including tumor marker assessment) will be performed every 8 weeks (Day 1 [±7 days] in odd number cycle) from Day 1 of Cycle 1, or more frequently if disease progression is clinically indicated.
k: Subjects will be hospitalized until completion of Cycle 1 in Part 1. Outpatient is allowed after C1D15 when investigator or subinvestigator judges that the subject's safety is ensured.
l: +3 days in C2D1 (Part 1 only)
m: Cycle 3 or later, test items can be omitted only when investigator or subinvestigator judges that that the subject's safety is ensured.
n: Predose
o: Data within 7 days before discontinuation, if available, can be used as the discontinuation data.
p: Data within 28 days before off treatment, if available, can be used as the discontinuation data.
q: If a new anticancer agent needs to be immediately started due to deterioration in the subject's condition, the last observation visit can be conducted before 30 days after the last dose of the study drug has passed but prior to starting the new anticancer agent. If the last observation visit occurs within 7 days after study drug discontinuation, discontinuation data can be used as the last observation data.
r: Only in Part 2. Every 12 weeks (±2 weeks) from last observation visit
s: Predose and just before completion of nivolumab administration
t: Predose of Cycles 2, 3, 4, 5, 9, 13 (thereafter every 4 cycles) and just before completion of nivolumab administration in Cycle 5
u: Predose of Cycle 5
v: Predose of Cycles 2, 3, 5, 9, 13 (thereafter every 4 cycles)
w: Part 2 only. Predose of Cycles 1 and 3. When the subject discontinues the study before sampling of Cycle 3, the sampling at discontinuation visit should be done.

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 SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

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

The detailed contact information for reporting of SAEs is provided in the Attachment.

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 or subinvestigator's assessment of causality.

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

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

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 5 months of last study treatment or 30 days following the last study treatment if the subject initiates new anticancer therapy, whichever is earlier, and any partner's pregnancy of male subjects in which the estimated date of conception is either before the last visit or within 30 days of last study treatment or 30 days following the 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 5 months of last study treatment or 30 days following the last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported.

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

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

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy or breastfeeding. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Attachment. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

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

9.5.4.3 Reporting of Events Associated with Special Situations

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

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

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

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the 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 CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigator, 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 the investigator provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

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

9.5.5 Completion/Discontinuation of Subjects

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

The investigator or subinvestigator 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 recorded on the CRF with the reason of discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator, subinvestigator, or clinical research coordinator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator, subinvestigator, or clinical research coordinator 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 or subinvestigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's 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. As defined by GCP, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

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

Completed, original CRFs are the sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor 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 after the data cutoff for 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

The endpoints of this study are shown below. All efficacy endpoints will be assessed using mRECIST. If necessary, RECIST1.1 will also be performed and used for analysis.

9.7.1.1.1 PRIMARY ENDPOINTS

- DLTs (Part 1 only)
- Safety endpoints including AEs, laboratory tests, vital signs, ECG, ECOG-PS, and LVEF

9.7.1.1.2 SECONDARY ENDPOINTS

- **ORR** is defined as the proportion of subjects who have BOR of CR or PR
- Pharmacokinetic parameters of lenvatinib and nivolumab

9.7.1.1.3 EXPLORATORY ENDPOINTS

CCI

[redacted]

9.7.1.2 Definitions of Analysis Sets

DLT Analysis Set will include all subjects (Part 1 only) who have completed Cycle 1 without major protocol deviation with at least 75% of lenvatinib compliance and at least 2 doses of nivolumab 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 will include all subjects who received at least 1 dose of lenvatinib or nivolumab.

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

The Efficacy Analysis Set will include all subjects who received at least 1 dose of lenvatinib and nivolumab.

The Pharmacodynamic and PGx Analysis Set is the group of subjects who received at least 1 dose of lenvatinib and nivolumab and had at least 1 postdose pharmacodynamic or PGx data.

9.7.1.3 Subject Disposition

Subjects who signed informed consent, failed screening and the reason for screen failures will be presented. Subjects who were treated, were not treated, completed the study, and discontinued the study and the reason for discontinuation will be presented. Similarly, subjects who completed the treatment, the reason for completion, discontinued the study treatment and the reason for discontinuation will be presented.

In this protocol, subjects who completed the study are defined as subjects who completed the appropriate DLT evaluation in Part 1 and subjects who completed the discontinuation assessment or last observation assessment in Part 2. Subjects who completed the study treatment are defined as who discontinued the treatment due to disease progression or subjects who are continuing the study treatment at the date of data cutoff.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized for each part. Continuous demographic and baseline variables include age, height, and weight; categorical variables include sex, age group (<65 years, ≥65 years), race, ethnics, ECOG-PS, and primary disease characteristics and prior therapies for primary disease.

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). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by part. Anatomical Therapeutic Chemical (ATC) class (eg, anatomical class, therapeutic class, pharmacologic class, chemical class, if feasible), and WHO DD preferred term. 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) or, started at the time of or after 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 conducted by part based on the Efficacy Analysis Set. Tumor assessment will be analyzed based on the investigator's assessment. If needed, the analysis based on independent review will be conducted.

Part 1

BOR will be summarized based on mRECIST, and ORR and their corresponding exact 2-sided 95% confidence interval (CI) will be calculated. DCR and CBR will be summarized in a same manner.

Part 2

In addition to the same analysis as above for Part 1, PFS will be summarized and plotted over time by Kaplan-Meier method. The median, first and third quartiles (Q1 and Q3) of PFS rate and the cumulative probability of PFS rate at selected time points with 2-sided 95% CI will be calculated, but not limited to. PFS censoring rules will be defined in the SAP and followed FDA guidance (2007). TTP, DOR, TTR, and OS will be summarized similarly. 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). A spider plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions.

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 by noncompartmental analysis using the PK analysis set (Part 1 only). If warranted, additional analyses may be performed. PK data for lenvatinib and nivolumab is planned to be analyzed using nonlinear mixed effects modeling. PK data for lenvatinib and nivolumab may also be used to explore the exposure-response relationships for antitumor activity/efficacy as well as biomarkers and safety, if feasible. The results of these analyses, if performed, will be reported separately.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The effect of lenvatinib-nivolumab combination therapy on soluble and/or tissue biomarkers will be summarized using descriptive statistics.

9.7.1.8 Safety/Tolerability Analyses

All DLT analyses will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated. DLT will also be summarized per type of toxicity. All other safety analyses will be performed on the Safety Analysis Set by part. Safety data will be summarized using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables).

9.7.1.8.1 EXTENT OF EXPOSURE

The number of cycles/days on treatment, sum of subject-time, number of administration, total amount of study drug administered, dose intensity, and relative dose intensity (actual dose/planned dose) will be summarized for lenvatinib and nivolumab separately.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using 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 treatment and until the 30 days after the last dose or until the subject initiates new anticancer therapy, whichever is earlier, 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 incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by MedDRA 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 of study drug, study drug dose reduction, and study drug interruption will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation of study drug, study drug dose reduction, and study drug interruption will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit 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 by visit and maximum postbaseline grades will be summarized. Shifts from Baseline CTCAE v4.03 grades to postbaseline grades will be presented.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. They will be shown in subject data listing.

CTCAE v4.03 will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs), if necessary.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, temperature), weight, and SPO_2 and changes from baseline will be presented by visit.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments performed at each visit will be used for evaluation. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia (QTcF) will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

9.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive statistics for LVEF and LVEF changes from baseline assessed by MUGA scans or echocardiograms will be summarized by visit.

ECOG-PS will be summarized by scale at each visit and by highest postbaseline scale.

9.7.1.9 Immunogenicity

All immunogenicity analyses will be performed using the Safety Analysis Set. The percentage and frequency of expression will be calculated for serum anti-nivolumab antibodies. If anti-nivolumab antibody develops, frequency and percentage for presence of neutralizing antibody will be summarized.

9.7.2 Determination of Sample Size

A sample size of approximately 26 subjects will be enrolled in this study; 6 patients for Part 1 and 20 patients for Part 2. Six subjects in Part 1 was deemed appropriate to evaluate the tolerability of the dose and perform preliminary safety assessment. Twenty subjects in Part 2 was determined to further evaluate the safety and preliminary efficacy. The probability to detect at least 1 development of intolerable treatment-related AEs with an incidence of 10%,

15% or 20% in 20 subjects was 87.8%, 96.1%, or 98.8%, respectively. Therefore, the sample size is determined to be approximately 20 subjects.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

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

10 REFERENCE LIST

El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389(10088):2492-502.

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

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved in writing by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs. 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 or subinvestigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor and the IRB for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to the IRB. In these cases, the sponsor may be required to send a letter to the head of the medical institution detailing such changes.

11.2 Adherence to the Protocol

The investigator or subinvestigator will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The head of the medical institution will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with 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 GCP. All records at the site are subject to inspection by the local auditing agency and to IRB review.

In accordance with GCP, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments
- 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
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs
- CRF components that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

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

11.5 Identification of Source Data

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

- Study drug administration (reason for treatment discontinuation, reason for dose modification. or others)
- Reasons for prior and concomitant therapy (including medications and therapies)
- Discontinuation (reason for discontinuation, or others)
- Sampling date and time for PK analysis
- Sampling date for clinical laboratory tests
- AEs (grade, relationship to study drug, outcome or others)
- Outcome of Follow-up when a subject stop visiting the site
- Race, ethnicity

For items except (1) to (6) below, the source documents are considered to be source data, but any appropriate document instead of source documents can be used as source data:

(1)Source data of informed consent

- Signed ICF

(2)Source data of histopathology

- Histopathology chart, patient referral document including electronic data

(3)Source data of tumor assessment

- Films including electronic data

  Note that findings and measurement recorded on the CRF are source data.

(4)Source data of ECGs

- ECG charts including electronic data

  Note that normal or abnormal findings recorded on the CRF are source data.

(5)Record of sample shipment to external vender

- Sample shipment slip

(6)Source data of relevant tests

- Clinical laboratory test chart including electronic data

11.6 Retention of Records

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

It is requested that at the completion of the required retention period the medical institution 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 GCP and all applicable local regulations. Government regulatory authority may request an inspection.

11.8 Handling of Study Drug

All study drugs will be supplied to the assigned pharmacist (or designee) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The assigned pharmacist (or designee) must maintain an accurate record of the shipment and dispensing of the study drug

in a drug accountability ledger. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The assigned pharmacist (or designee) must not destroy any drug labels or discard 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 assigned pharmacist (or designee) will return all used study drugs and a copy of the completed drug disposition form to the sponsor, if required.

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. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

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

11.10 Disclosure and Confidentiality

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

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

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/the head of the medical institution and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the

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

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/the head of medical institution should promptly inform the sponsor and the IRB and provide the sponsor and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted in 11.6 Retention of Records 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.

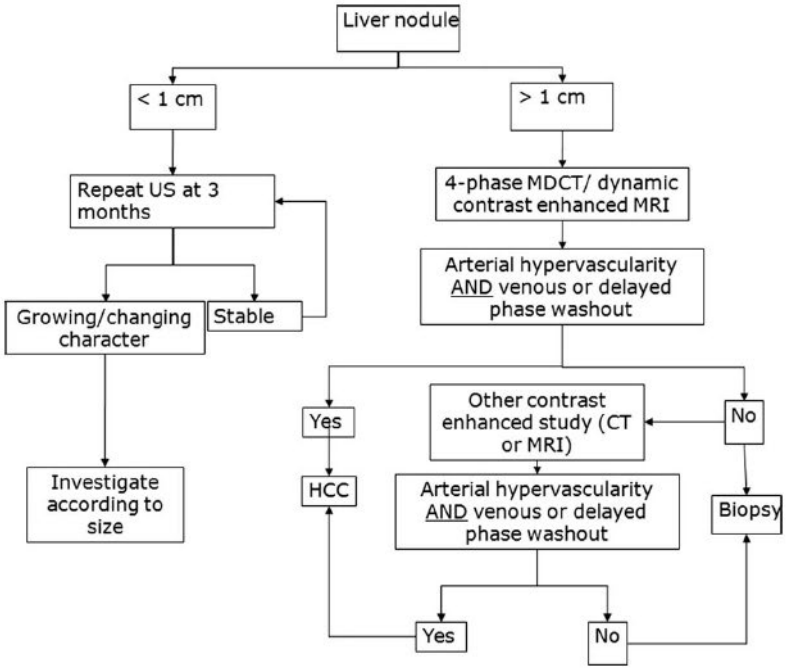


Fig. 1. Diagnostic algorithm for suspected HCC. CT, computed tomography; MDCT, multidetector CT; MRI, magnetic resonance imaging; US, ultrasound.

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. The target and nontarget categories are classified into 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 one 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 (i.e., 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 (e.g., < 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

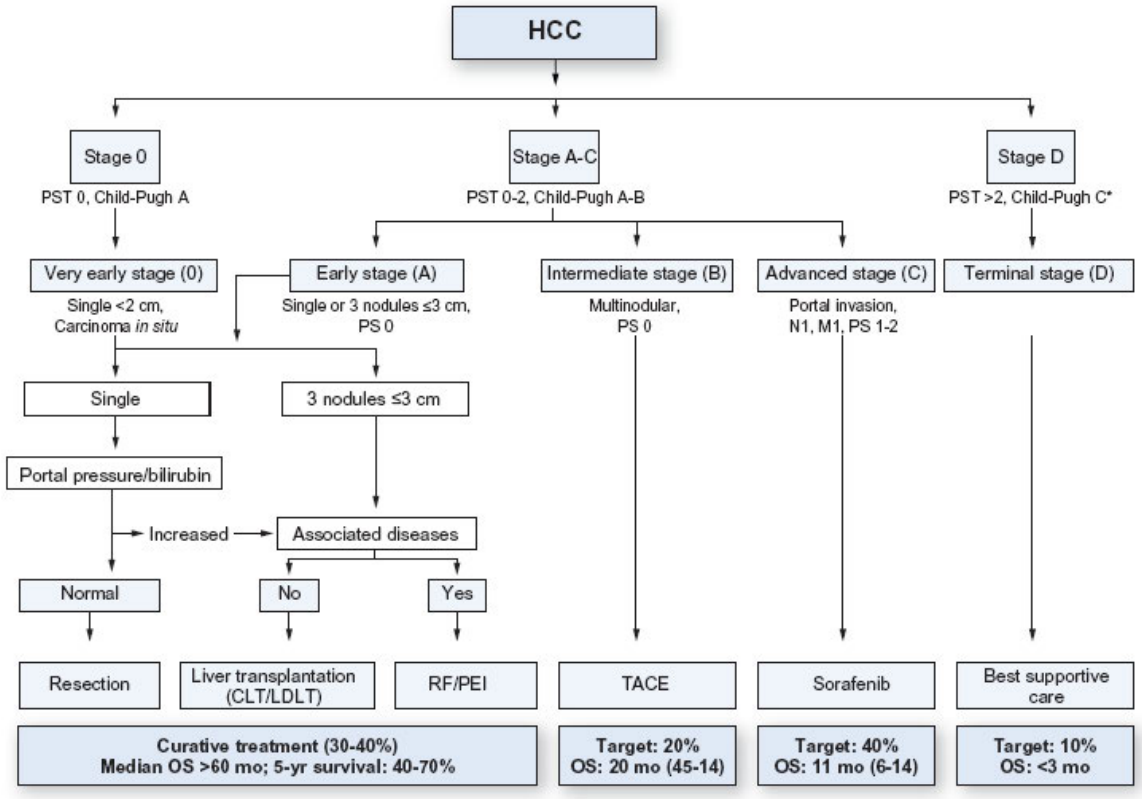


Fig. 3. Updated BCLC staging system and treatment strategy, 2011.

☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2011.12.001.
* Correspondence: EASL Office, 7 rue des Battoirs, CH-1205 Geneva, Switzerland. Tel.: +41 22 807 0360; fax: +41 22 328 0724.
E-mail address: easloffice@easloffice.eu (European Association for the Study of the Liver).

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. In press. http://www.easl.eu/_clinical-practice-guideline/issue-7-April-2012-management-of-hepatocellular-carcinoma

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 (e.g., 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 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.

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 7 Tumor, Node, and Metastasis (TNM) Staging of Hepatocellular Carcinoma

The TNM 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.

Protocol Change Tracking

Study Protocol Title: A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Study Protocol Number: E7080-J081-117

Section	Original Text (Version 7.0, 14 Feb 2020)	Amended Text (Version 8.0, 05 Feb 2021)	Reason of Amendment(s)
2	**Exclusion Criteria** 31. Women of childbearing potential or men of impregnate potential who don't agree that both the subject and her partner will use the following methods of contraception for periods from before informed consent to during the clinical study and 5 months later (for male subjects 7 months) from last administration of study drug.	**Exclusion Criteria** 31. Women of childbearing potential or men of impregnate potential who don't agree that both the subject and her partner will use the following methods of contraception for periods from before informed consent to during the clinical study and 5 months later (for male subjects 30 days) from last administration of study drug.	Amendment according to the change of addendum of nivolumab investigator's brochure
9.1.3.3	(omission) In Part 2, all subjects will be followed for survival until death every 12 weeks (±2 week) from the date of discontinuation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2.	(omission) In Part 2, all subjects will be followed for survival until death every 12 weeks (±2 week) from the date of discontinuation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued until discontinuation of the last subject or for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2, whichever occurs later.	Change of survival follow-up duration
9.3.2	31. Women of childbearing potential or men of impregnate potential who don't agree that both the subject and her partner will use the following methods of contraception for periods from before informed consent to during the clinical study and 5 months later (for male subjects 7 months) from last administration of study drug.	31. Women of childbearing potential or men of impregnate potential who don't agree that both the subject and her partner will use the following methods of contraception for periods from before informed consent to during the clinical study and 5 months later (for male subjects 30 days) from last administration of study drug.	Amendment according to the change of addendum of nivolumab investigator's brochure

Section	Original Text (Version 7.0, 14 Feb 2020)	Amended Text (Version 8.0, 05 Feb 2021)	Reason of Amendment(s)
9.3.3	(omission) In Part 2, all subjects will be followed for survival until death every 12 weeks (±2 week) from the date of discontinuation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2.	(omission) In Part 2, all subjects will be followed for survival until death every 12 weeks (±2 week) from the date of discontinuation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued <u>until discontinuation of the last subject or</u> for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2<u>, whichever occurs later</u>.	Change of survival follow-up duration
9.5.1.3.3	Subjects will be followed for survival until death every 12 weeks (±2 week) from the date of last observation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2.	Subjects will be followed for survival until death every 12 weeks (±2 weeks) from the date of last observation, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up. The survival follow-up will be continued <u>until discontinuation of the last subject or</u> for up to 2 years after Cycle 1 Day 1 of the last subject enrolled in Part 2<u>, whichever occurs later</u>.	Change of survival follow-up duration
9.5.1.4.2.2	(omission) At the end of the analysis, results may be presented in the clinical study 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.	(omission) At the end of the analysis, results may be presented in the clinical study report <u>or a separate report</u> 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.	To adjust the description.

Section	Original Text (Version 7.0, 14 Feb 2020)	Amended Text (Version 8.0, 05 Feb 2021)	Reason of Amendment(s)
9.5.4.2	Any pregnancy in which the estimated date of conception is either before the last visit or within 5 months of last study treatment or 30 days following the last study treatment if the subject initiates new anticancer therapy, whichever is earlier, and any partner's pregnancy of male subjects in which the estimated date of conception is either before the last visit or within 7 months of last study treatment or 30 days following the 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 5 months of last study treatment or 30 days following the last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported.	Any pregnancy in which the estimated date of conception is either before the last visit or within 5 months of last study treatment or 30 days following the last study treatment if the subject initiates new anticancer therapy, whichever is earlier, and any partner's pregnancy of male subjects in which the estimated date of conception is either before the last visit or within 30 days of last study treatment or 30 days following the 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 5 months of last study treatment or 30 days following the last study treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported.	Amendment according to the change of addendum of nivolumab investigator's brochure
9.7	All statistical analyses will be performed after the database is locked. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).	All statistical analyses will be performed after the data cutoff for 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).	To adjust the description.

Protocol Change Tracking

Study Protocol Title: A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Study Protocol Number: E7080-J081-117

Section	Original Text (Version 6.0, 22 Nov 2019)	Amended Text (Version 7.0, 14 Feb 2020)	Reason of Amendment(s)
2	**Study Period and Phase of Development** Approximately 30 months Phase 1b	**Study Period and Phase of Development** Approximately 45 months Phase 1b	Because it is expected that there will be subjects who continue to receive the study treatment at "approximately 30 months" after the start of the study.
7	ONO-4538/nivolumab is a human anti-human programmed death-1 (PD-1, also known as CD279) monoclonal antibody, developed by Ono Pharmaceutical and Medarex (current Bristol-Myers Squibb). Clinical development program of nivolumab is currently underway by Ono Pharmaceutical and Bristol-Myers Squibb. Nivolumab is approved in many countries including the United States, European Union, and Japan. However, nivolumab is not approved in subjects with HCC anywhere in the world. The preliminary results from the multinational Phase 1/2 study (CA209040 study) for HCC subjects showed favorable efficacy and safety profile (El-Khoueiry AB, et al., 2017). A phase 3 randomized study of nivolumab compared with sorafenib in the first-line treatment of subjects with advanced HCC (ONO-4538-35/CA209459) is ongoing.	ONO-4538/nivolumab is a human anti-human programmed death-1 (PD-1, also known as CD279) monoclonal antibody, developed by Ono Pharmaceutical and Medarex (current Bristol-Myers Squibb). Clinical development program of nivolumab is currently underway by Ono Pharmaceutical and Bristol-Myers Squibb. Nivolumab is approved in many countries including the United States, European Union, and Japan. Nivolumab monotherapy has shown clinical benefit in HCC patients who have previously been treated with sorafenib and has been approved for use in the United States and elsewhere. In addition, an international phase 3 study comparing nivolumab and sorafenib in progressed HCC patients who have not been treated with systemic chemotherapy (ONO-4538-35 / CA209459), and an international phase 3 study comparing the combination of	To reflect the latest information on nivolumab.

Section	Original Text (Version 6.0, 22 Nov 2019)	Amended Text (Version 7.0, 14 Feb 2020)	Reason of Amendment(s)
		nivolumab and ipilimumab with sorafenib or lenvatinib in progressed HCC patients who have not been treated (ONO 4538−92/CA2099DW) is currently ongoing.	
9.4.4	Based on these efficacy and safety data, ONO-4538 3 mg/kg IV every 2 weeks is being studied in clinical studies in subjects with melanoma, NSCLC, RCC, classical Hodgkin's lymphoma, and head and neck cancer. Recently, the use of flat dosing of ONO-4538, without body-weight normalizing, is being investigated to improve ease of administration. Clinical studies in subjects with ovarian cancer, esophageal cancer, and HCC are ongoing at a flat dose of 240 mg every 2 weeks.	Based on these efficacy and safety data, ONO-4538 3 mg/kg IV every 2 weeks is being studied in clinical studies in subjects with multiple tumor types. Recently, the use of flat dosing of ONO-4538, without body-weight normalizing, is being investigated to improve ease of administration. Clinical studies in subjects with multiple tumor types are ongoing at a flat dose of 240 mg every 2 weeks and 480 mg every 4 weeks.	To reflect the latest information on nivolumab.
9.5.1.4.1	**Blood Sampling Day (Part 1)** Thereafter Day 1 of every Cycle	**Blood Sampling Day (Part 1)** Thereafter Day 1 of every Cycle [a] a: Blood collection is not required after the 24th cycle [Added in Version 7.0]	It was determined that the drug concentration data obtained so far for Part 1 subjects allow for sufficient evaluation of trough value fluctuations during long-term administration.
9.5.2.1	i: For Part 1, blood collection at predose, 1, 2, 4, 8, 24 hours postdose of Cycle 1 Day1 and Day 15, and predose of Day 1 of every cycle thereafter. For Part 2, blood collection at 0.5 - 4 hours postdose of Cycle1 Day1, pre and 0.5 - 4 hours postdose of Cycle1 Day15 and predose of Cycles 2, 4, 6	i: For Part 1, blood collection at predose, 1, 2, 4, 8, 24 hours postdose of Cycle 1 Day1 and Day 15, and predose of Day 1 of every cycle thereafter. However, blood collection is not required after Cycle 24. For Part 2, blood collection at 0.5 - 4 hours postdose of Cycle1 Day1, pre and 0.5 - 4 hours postdose of Cycle1 Day15 and predose of Cycles 2, 4, 6	It was determined that the drug concentration data obtained so far for Part 1 subjects allow for

Section	Original Text (Version 6.0, 22 Nov 2019)	Amended Text (Version 7.0, 14 Feb 2020)	Reason of Amendment(s)
			sufficient evaluation of trough value fluctuations during long-term administration.
9.7.1.1.2	• ORR is defined as the proportion of subjects who have BOR of CR or PR • Pharmacokinetic parameters of lenvatinib	• ORR is defined as the proportion of subjects who have BOR of CR or PR • Pharmacokinetic parameters of lenvatinib and nivolumab	Correction of errors

Protocol Change Tracking

Study Protocol Title: A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Study Protocol Number: E7080-J081-117

Section	Original Text (Version 5.0, 19 Jul 2019)	Amended Text (Version 6.0, 22 Nov 2019)	Reason of Amendment(s)
2	**Exclusion Criteria** (Not stated)	**Exclusion Criteria** 32. Participants who have received a live/attenuated vaccine within 28 days of first dose of study drugs	To consider the possibility to affect the safety assessments of nivolumab.
	Prohibited Concomitant Medications/Therapies (Not stated)	**Prohibited Concomitant Medications/Therapies** Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) are prohibited during treatment and until 30 days post last dose.	
9.3.2	**Exclusion Criteria** (Not stated)	**Exclusion Criteria** 32. Participants who have received a live/attenuated vaccine within 28 days of first dose of study drugs	
9.4.7.2	**Prohibited Concomitant Therapies and Drugs** (Not stated)	**Prohibited Concomitant Therapies and Drugs** Any live/attenuated vaccine (eg, varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella [MMR]) are prohibited during treatment and until 30 days post last dose.	

Protocol Change Tracking

Study Protocol Title: A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Study Protocol Number: E7080-J081-117

Section	Original Text (Version 4.0, 27 Aug 2018)	Amended Text (Version 5.0, 19 Jul 2019)	Reason of Amendment(s)
9.5.1.5.3	**Table 8 Clinical Laboratory Tests** Chemistry: Other Glucose, albumin, total cholesterol, triglycerides, phosphorus, lactate dehydrogenase, total protein, sodium, potassium, chloride, calcium, magnesium, ammonia[b], amylase[c], lipase[c]	**Table 8 Clinical Laboratory Tests** Chemistry: Other Glucose, albumin, total cholesterol, triglycerides, phosphorus, lactate dehydrogenase, total protein, sodium, potassium, chloride, calcium, magnesium, ammonia[b], amylase[c], lipase[c], ACTH[e], cortisol[e] e: If necessary, appropriate laboratory tests such as adrenal cortical function test (ACTH, cortisol) to be added.	To reflect the revision* of nivolumab package insert as of 09 May 2019. * Hepatic failure and pituitary dysfunction were added to the section of "Clinically Significant Adverse Reactions" of the package insert.
9.5.2.1	**Table 9 Schedule of Procedures/Assessments in Study E7080-J081-117 (for Part 1 and Part 2)** c: Virus test (Screening only, Data within 28 days before the first dose can be used), Ammonia test (Screening only), Hematology, blood chemistry, urinalysis, blood coagulation tests, thyroid function test.	**Table 9 Schedule of Procedures/Assessments in Study E7080-J081-117 (for Part 1 and Part 2)** c: Virus test (Screening only, Data within 28 days before the first dose can be used), Ammonia test (Screening only), Hematology, blood chemistry, urinalysis, blood coagulation tests, thyroid function test. If necessary, appropriate laboratory tests such as adrenal cortical function test (ACTH, cortisol) to be added.	

Protocol Change Tracking

Study Protocol Title: A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Study Protocol Number: E7080-J081-117

Section	Original Text (Version 3.0, 07 May 2018)	Amended Text (Version 4.0, 27 Aug 2018)	Reason of Amendment(s)
2 9.3.2	**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	**Exclusion Criteria** 1. Imaging findings for HCC corresponding to any of the following (Part 1 only): • HCC with ≥50% liver occupation • Clear invasion into the bile duct • Portal vein invasion with Vp4	To confirm the safety/efficacy in the subject group in the left column. It was determined that the criteria have no significant impact on subject safety because it is used to ensure uniformity of subject backgrounds.
2	**2. Cycle 2 and onward (and applies to Cycle 1 and onward of part 2)** Relationship to lenvatinib and/or nivolumab will be evaluated, then necessity of dose modification (either or both drugs) will be determined. Dose adjustment for management of intolerable toxicities will be made according to the guidelines provided in the table below. a: An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) will require discussion with the sponsor before treatment can be resumed. During treatment interruption, repeat AEs assessment at least every	**2. Cycle 2 and onward (and applies to Cycle 1 and onward of part 2)** Relationship to lenvatinib and/or nivolumab will be evaluated, then necessity of dose modification (either or both drugs) will be determined. Dose adjustment for management of intolerable toxicities will be made according to the guidelines provided in the table below. a: An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) will require discussion with the sponsor before treatment can be resumed. During treatment interruption, repeat AEs assessment about every	To review the assessment period during the interruption of lenvatinib.

Section	Original Text (Version 3.0, 07 May 2018)	Amended Text (Version 4.0, 27 Aug 2018)	Reason of Amendment(s)
	7 days (until restarting administration).	7 days (until restarting administration).	
9.4.1.3.2.1	**Table 2 Dose Adjustments of Lenvatinib** a: An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) will require discussion with the sponsor before treatment can be resumed. During treatment interruption, repeat AEs assessment at least every 7 days (until restarting administration).	**Table 2 Dose Adjustments of Lenvatinib** a: An interruption of lenvatinib for more than 28 days (due to treatment-related toxicities) will require discussion with the sponsor before treatment can be resumed. During treatment interruption, repeat AEs assessment about every 7 days (until restarting administration).	
Table 9	[Footnote] w: Predose of Cycles 1 and 3. When the subject discontinues the study before sampling of Cycle 3, the sampling at discontinuation visit should be done.	[Footnote] w: Part 2 only. Predose of Cycles 1 and 3. When the subject discontinues the study before sampling of Cycle 3, the sampling at discontinuation visit should be done.	To clarify the description.

Protocol Change Tracking

Study Protocol Title: A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Study Protocol Number: E7080-J081-117

<table>
<tr><th>Section</th><th>Original Text (Version 2.0, 09 Jan 2018)</th><th>Amended Text (Version 3.0, 07 May 2018)</th><th>Reason of Amendment(s)</th></tr>
<tr><td>2

9.7.1.7.1</td><td>The primary PK parameters of lenvatinib in the combination will be calculated by noncompartmental analysis using the PK analysis set.</td><td>The primary PK parameters of lenvatinib in the combination will be calculated by noncompartmental analysis using the PK analysis set <u>(Part 1 only)</u>.</td><td rowspan="2">To review the analysis in Part 2 according to the accumulation of pharmacokinetic information on lenvatinib.</td></tr>
<tr><td>9.5.1.4.1</td><td>Table 5 Blood Sampling Schedule for Pharmacokinetic Assessment of Lenvatinib
<table>
<tr><th>Day</th><th>Sampling Time</th><th>Allowance (as a Target)</th></tr>
<tr><td>Cycle 1 Day 1</td><td>Predose of nivolumab</td><td>Within –60 minutes before dosing</td></tr>
<tr><td></td><td>1 hour postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>2 hours postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>4 hours postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>8 hours postdose of lenvatinib</td><td>±60 minutes</td></tr>
<tr><td>Cycle 1 Day 2</td><td>Predose of lenvatinib (24 hours postdose)</td><td>Within –60 minutes before dosing</td></tr>
<tr><td>Cycle 1 Day 15</td><td>Predose of lenvatinib</td><td>Within –60 minutes before dosing</td></tr>
<tr><td></td><td>1 hour postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>2 hours postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>4 hours postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>8 hours postdose of lenvatinib</td><td>±60 minutes</td></tr>
<tr><td>Cycle 1 Day 16</td><td>Predose of lenvatinib (24 hours postdose)</td><td>Within –60 minutes before dosing</td></tr>
</table></td><td>Table 5 Blood Sampling Schedule for Pharmacokinetic Assessment of Lenvatinib
<table>
<tr><th><u>Day (Part 1)</u></th><th>Sampling Time</th><th>Allowance (as a Target)</th></tr>
<tr><td>Cycle 1 Day 1</td><td>Predose of nivolumab</td><td>Within –60 minutes before dosing</td></tr>
<tr><td></td><td>1 hour postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>2 hours postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>4 hours postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>8 hours postdose of lenvatinib</td><td>±60 minutes</td></tr>
<tr><td>Cycle 1 Day 2</td><td>Predose of lenvatinib (24 hours postdose)</td><td>Within –60 minutes before dosing</td></tr>
<tr><td>Cycle 1 Day 15</td><td>Predose of lenvatinib</td><td>Within –60 minutes before dosing</td></tr>
<tr><td></td><td>1 hour postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>2 hours postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>4 hours postdose of lenvatinib</td><td>±15 minutes</td></tr>
<tr><td></td><td>8 hours postdose of lenvatinib</td><td>±60 minutes</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Section</th><th>Original Text (Version 2.0, 09 Jan 2018)</th><th>Amended Text (Version 3.0, 07 May 2018)</th><th>Reason of Amendment(s)</th></tr>
<tr><td></td><td>
<table>
<tr><td>Thereafter Day 1 of every Cycle</td><td>Predose of lenvatinib</td><td>–</td></tr>
</table>
</td><td>
<table>
<tr><td>Cycle 1 Day 16</td><td>Predose of lenvatinib (24 hours postdose)</td><td>Within –60 minutes before dosing</td></tr>
<tr><td>Thereafter Day 1 of every Cycle</td><td>Predose of lenvatinib</td><td>–</td></tr>
</table>
<table>
<tr><th><u>Day (Part 2)</u></th><th><u>Sampling Time</u></th><th><u>Allowance (as a Target)</u></th></tr>
<tr><td><u>Cycle 1 Day 1</u></td><td><u>0.5 – 4 hour postdose of lenvatinib</u></td><td><u>–</u></td></tr>
<tr><td rowspan="2"><u>Cycle 1 Day 15</u></td><td><u>Predose of lenvatinib</u></td><td><u>–</u></td></tr>
<tr><td><u>0.5 – 4 hour postdose of lenvatinib</u></td><td><u>–</u></td></tr>
<tr><td><u>Day 1 of Cycles 2, 4, 6</u></td><td><u>Predose of lenvatinib</u></td><td><u>–</u></td></tr>
</table>
</td><td></td></tr>
<tr><td>9.5.1.4.2.1</td><td>Blood samples for the development of exploratory biomarkers will be collected from all consented subjects at designated time points as specified in the Schedule of Procedures/Assessments (Table 9).</td><td>Blood samples for the development of exploratory biomarkers will be collected from all consented subjects at designated time points as specified in the Schedule of Procedures/Assessments (Table 9) <u>(blood samples for nivolumab will be collected in Part 2 only).</u></td><td>To review the biomarker blood sampling schedule.</td></tr>
<tr><td>9.5.1.5.3</td><td>Virus tests[b] in Table 8
b: Screening only.</td><td>Virus tests[b] in Table 8
b: Screening only. <u>Data within 28 days before the first dose can be used.</u></td><td rowspan="2">It was reviewed based on turnaround time of clinical laboratory results.</td></tr>
<tr><td>9.5.1.5.9.2</td><td>Hepatitis B surface (HBs) antigen, HBs antibody, hepatitis B virus core (HBc) antibody, hepatitis C virus (HCV) antibody, HBV-DNA, HCV-RNA, HDV antibody or HDV RNA (hepatitis B only), and HIV antibody tests will be performed at Screening.</td><td>Hepatitis B surface (HBs) antigen, HBs antibody, hepatitis B virus core (HBc) antibody, hepatitis C virus (HCV) antibody, HBV-DNA, HCV-RNA, HDV antibody or HDV RNA (hepatitis B only), and HIV antibody tests will be performed at Screening. <u>Data within 28 days before the first dose can be used.</u></td></tr>
</table>

Section	Original Text (Version 2.0, 09 Jan 2018)	Amended Text (Version 3.0, 07 May 2018)	Reason of Amendment(s)
9.5.1.5.4	Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], body temperature [in centigrade]), and weight (kg) and percutaneous oxygen saturation (SPO2) 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 sitting after the subject has been resting. All BP measurements should be performed on the same arm, preferably by the same person. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. For subjects with an elevated BP (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), confirmation should be obtained by performing 2 measurements a minimum of 1-hour apart.	Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], body temperature [in centigrade]), and weight (kg) and percutaneous oxygen saturation (SPO2) 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 sitting after the subject has been resting. All BP measurements should be performed on the same arm, preferably by the same person.	To adjust the description according to the protocol revision (Ver. 2.0).
Table 9	[Endpoints] Lenvatinib PK blood sampling: PD biomarker blood sampling: [Footnotes] c: Virus test (Screening only), Ammonia test (Screening only), hematology, blood chemistry, urinalysis, blood coagulation tests, thyroid function test. i: Blood collection at pre, 1, 2, 4, 8, 24 hours post-dose l: +3 days in C2D1	[Endpoints] Lenvatinib PK blood sampling: Change its footnote for Cycle 2 or later from n to i. Lenvatinib PD biomarker blood sampling: Eliminate Day 15 assessment in Cycle 2 or later. Nivolumab PD biomarker blood sampling: Add assessments to Day 1 in Cycle 1, Day 1 in Cycle 2 or later, and Discontinuation. [Footnotes] c: Virus test (Screening only, Data within 28 days before the first dose can be used), Ammonia test (Screening only), hematology, blood chemistry, urinalysis, blood coagulation tests, thyroid function test. i: For Part 1, blood collection at predose, 1, 2, 4, 8, 24 hours postdose of Cycle 1 Day1 and Day 15, and predose of Day 1 of every cycle thereafter. For Part 2, blood collection at 0.5 – 4 hours postdose of Cycle 1 Day1, pre and 0.5 – 4 hours postdose of Cycle 1 Day 15 and predose of Cycles 2, 4, 6. l: +3 days in C2D1 (Part 1 only)	Due to review based on turnaround time of in-site clinical laboratory results, review of pharmacokinetic analysis on lenvatinib, and reconsideration of the biomarker blood sampling schedule, etc.

Section	Original Text (Version 2.0, 09 Jan 2018)	Amended Text (Version 3.0, 07 May 2018)	Reason of Amendment(s)
		w: Predose of Cycles 1 and 3. When the subject discontinues the study before sampling of Cycle 3, the sampling at discontinuation visit should be done.	

Protocol Change Tracking

Study Protocol Title: A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma

Study Protocol Number: E7080-J081-117

Section	Original Text (Version 1.0, 26 Sep 2017)	Amended Text (Version 2.0, 09 Jan 2018)	Reason of Amendment(s)
2 9.3.2	18. Subjects with a history of coinfection with both hepatitis B and C, including, but not limited to: 1)HBV DNA positive or HBV surface antigen positive subjects with detectable HCV antibody, OR 2)HCV RNA positive subjects with resolved HBV infection as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen, OR 3)Any positive test for HBV excluding HBV surface antibody indicating chronic or resolved HBV infection (positive HBV core antibody, positive HBV surface antigen, or detectable HBV DNA) and any positive test for HCV indicating chronic or resolved infection (positive HCV antibody or detectable HCV RNA)	(Not stated)	Amendment due to feedback from the investigator or subinvestigator and accumulation of experience to administer nivolumab
2 9.4.7.2	Antiplatelet agents	Antiplatelet agents and anticoagulants that require INR monitoring, such as warfarin (treatments that do not require INR monitoring, such as low molecular weight heparin and certain factor X inhibitors are permitted).	To ensure the consistency with No. 12 of the exclusion criteria, and other studies of lenvatinib for HCC.
9.4.1.4	Guidelines for assessment and management of hypertension are summarized as follows.	Guidelines for assessment and management of hypertension are summarized as follows. CTCAE v4.03 grading for	Amendment according to

Section	Original Text (Version 1.0, 26 Sep 2017)	Amended Text (Version 2.0, 09 Jan 2018)	Reason of Amendment(s)
	1. One blood pressure (BP) assessment is defined as the mean value of three measurements at least 5 minutes apart. 2. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is firstly observed on 2 measurements 1 hour apart. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensives should be added. 3. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg continues despite optimal management of hypertension, lenvatinib should be interrupted and resumed according to Table 3 at a dose of one-dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours. 4. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs despite the optimal management of hypertension, one-dose level reduction should be attempted. 5. Discontinue lenvatinib administration when Grade 4 hypertension (life-threatening) is present	hypertension will be based on BP measurements only (and not on the number of antihypertensive medications). 1. When blood pressure (BP) is elevated (systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg), BP measurement should be repeated at least 5 min apart. In this case, BP assessment is defined as the mean value of two measurements at least 5 minutes apart. 2. When systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is observed in the 1st BP assessment, the 2nd BP assessment should be repeated at least 30 min apart. The 2nd BP assessment is defined as the mean value of two measurements at least 5 minutes apart. For previously normotensive subjects, monotherapy with one of the classes of antihypertensives should be started when systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is firstly observed on the 2nd BP assessment. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or one or more agents of a different class of antihypertensives should be added. 3. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg continues despite optimal management of hypertension, lenvatinib should be interrupted and resumed according to Table 3 at a dose of one-dose level reduction only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours. 4. If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs despite the optimal management of hypertension, one-dose level reduction should be attempted. 5. Discontinue lenvatinib administration when Grade 4 hypertension (life-threatening) is present.	review of management of hypertension based on the accumulation of experience with lenvatinib administration.

Section	Original Text (Version 1.0, 26 Sep 2017)	Amended Text (Version 2.0, 09 Jan 2018)	Reason of Amendment(s)
9.5.1.4.2.2	**Security of the Samples, Use of the Samples, and Retention of the Samples** Samples will be stored until the finalization of the analytical report at the central laboratory. At the end of the storage period, samples will be destroyed.	**Security of the Samples, Use of the Samples, and Retention of the Samples** Samples will be stored for up to 15 years after the completion of the study. At the end of the storage period, samples will be destroyed. Samples may be stored longer if a Heath Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, samples will be stored until the questions have been adequately addressed.	To allow long-term sample retention, considering responses to authorities in the future.