16.1.9 Documentation of Statistical Methods

Listed below are all versions of the Statistical Analysis Plan for this study. The corresponding documents are provided on the following pages.

Statistical Analysis Plan	Version	Date
Revised original	V2.0	21 Apr 2023
Original	V1.0	17 Jan 2018

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7080-J081-117
Study Protocol Title:	A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma
Date:	21 Apr 2023
Version:	Version 2.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
AFP	α-fetoprotein
ATC	anatomical therapeutic chemical
BCLC	Barcelona Clinic Liver Cancer
BLQ	below lower quantification
BMI	body mass index
BOR	best overall response
BW	body weight
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	common toxicity criteria for adverse events
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HCC	hepatocellular carcinoma
IV	Intravenous
LLOQ	lower limit of quantification
LLT	lower level term
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multiple-gated acquisition technique
NE	not evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PD	progressive disease

Abbreviation	Term
PFS	progression free survival
PGx	pharmacogenomics
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
QD	every day
QOD	every other day
QTcF	QT interval corrected for heart rate using Fridericia's formula
Q2W	every 2 weeks
RECIST	response evaluation criteria in solid tumor
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SD	standard deviation
SI	système international
SOC	system organ class
SpO_2	percutaneous oxygen saturation
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TLG	tables, listings, and graphs
TNM	tumor, nodes, metastasis
TTP	time to progression
TTR	time to response
WHO DD	World Health Organization drug dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E7080-J081-117.

3.1 Study Objectives

3.1.1 Primary Objective

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

3.1.2 Secondary Objectives

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

3.1.3 Exploratory Objective

CCI

[redacted]

3.2 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 HCC for which no other appropriate therapy

is available. Part 2 is to further characterize the safety and tolerability and to assess preliminary efficacy of the combination therapy in HCC with no prior systemic therapy.

3.2.1 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 is 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])

The tolerability will be reviewed based on Dose Limiting Toxicity (DLT) of Cycle 1 (4 weeks) according to the following procedures.

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 investigators.

(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.

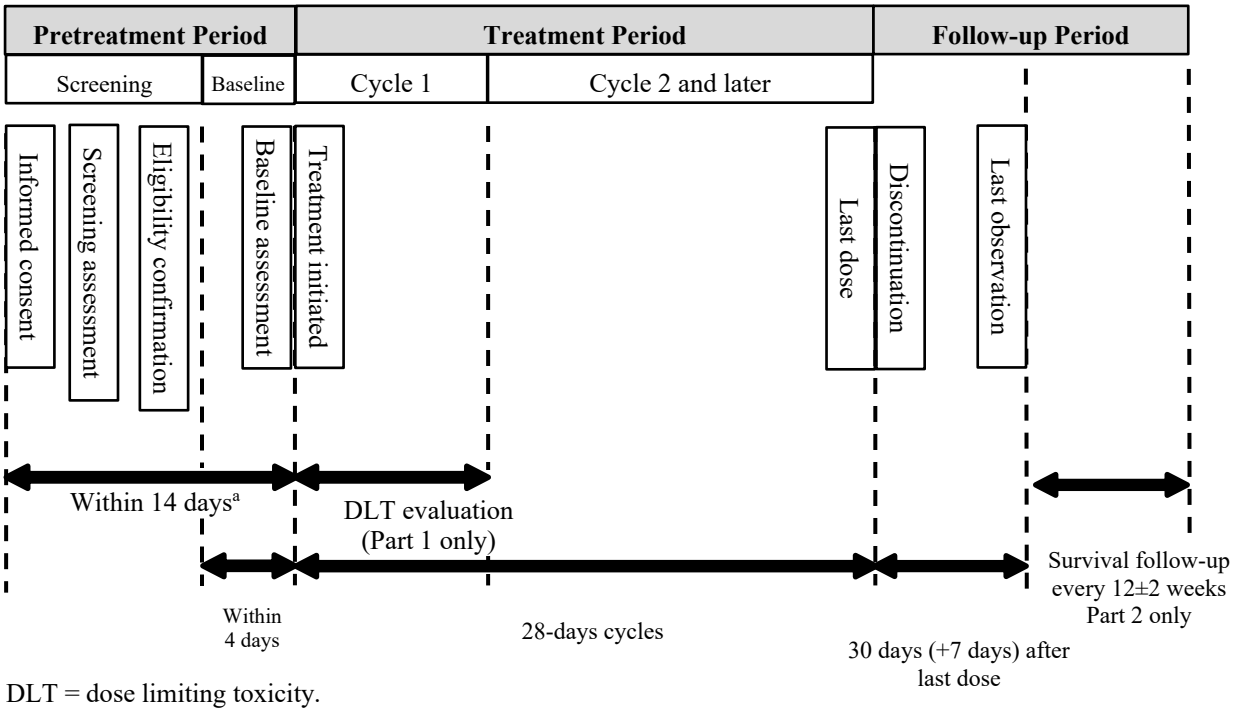
In this dose level, at least 3 subjects treated with lenvatinib 12 mg (BW ≥60 kg) and nivolumab need to be included in the 6 subjects for DLT evaluation. If this dose level is not tolerable, upon discussions between the sponsor, sponsor's responsible medical officer, and investigators, the lower dose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

3.2.2 Part 2

If the dose level is confirmed to be tolerable, 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.

3.2.3 Study Design

An overview of the study design is presented in Figure 1. Part 1 and Part 2 will consist of a pretreatment period, a treatment period, and a follow-up period.



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.)

Figure 1 Study Design

3.2.3.1 Pretreatment Period

The pretreatment period 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 Period.

3.2.3.2 Treatment Period

In the Treatment Period, subjects will receive lenvatinib in combination with nivolumab. The Treatment Period will begin with the first dose of study drug administration on Cycle 1

Day 1. Each cycle is 28 days long and subjects continue treatment until they meet any of the criteria in "Discontinuation Criteria by Subject (see Protocol Section 9.3.3.1)".

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

3.2.3.3 Follow-up Period

The follow-up period will consist of the examination at study discontinuation and the last observation visit which occurs 30 days after final administration of study drug. If the last observation visit occurs within 7 days after study drug discontinuation, discontinuation data can be used as the last observation data. 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 the new anticancer agent.

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.

4 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 26 subjects will be enrolled in this study, 6 subjects 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 true 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.

5 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the data cutoff for 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.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

All statistical analysis will be performed by part separately. Summarization for lenvatinib 8 mg group, 12 mg group and total subjects will be presented.

5.1 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.

5.1.1 Primary Endpoints

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

5.1.2 Secondary Endpoints

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

5.1.2.1 Pharmacokinetic (PK) Endpoints

PK parameters derived by non-compartmental analysis using plasma concentrations of lenvatinib (Part 1) which include, but are not limited to, are shown as below:

C_{max}	maximum observed concentration
t_{max}	time at which the highest drug concentration occurs
$AUC_{(0\text{-}t)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
$AUC_{(0\text{-}inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$t_{½}$	terminal elimination phase half-life
CL/F	apparent total clearance following oral dosing
V_z/F	apparent volume of distribution at terminal phase

MRT	mean residence time
$C_{ss,max}$	maximum observed concentration at steady state
$C_{ss,min}$	minimum observed concentration at steady state
$t_{ss,max}$	time at which the highest drug concentration occurs at steady state
$AUC_{(0-\tau)}$	area under the concentration-time curve over the dosing interval
CL_{ss}/F	apparent total clearance following oral administration at steady state
$C_{ss,av}$	average steady-state concentration
$R_{ac}(C_{max})$, $R_{ac}(AUC)$	accumulation index
PTF ratio	peak-trough fluctuation ratio

5.1.3 Exploratory Endpoints

CCI

CCI [redacted]

5.2 Study Subjects

5.2.1 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, or 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 for Lenvatinib will include all subjects who have received at least 1 dose of lenvatinib and nivolumab, and have evaluable concentration data of lenvatinib.

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

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.

The number of subjects enrolled (ie, subjects who signed informed consent), the number (percentage) of subjects included in each analysis set will be presented. Subject data listings will be provided.

5.2.2 Subject Disposition

For the summary table of screening subjects, the number (percentage) of subjects who were enrolled, continued in the study after screening, failed screening, and the primary reason for screen failures will be presented.

For the summary of the subject disposition, the number (percentage) of subjects who were treated/not treated, completed/discontinued the study, and the reason for the study discontinuation will be presented. Similarly, the number (percentage) of subjects who completed/discontinued the study treatment, and the reason for the discontinuation from study treatment will also be summarized. The number (percentage) of subjects who discontinued either lenvatinib alone or nivolumab alone and the reason for discontinuation will be summarized.

In this protocol, subjects who completed the study are defined as subjects who completed the appropriate DLT evaluation in Part 1, or 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.

Subject data listings will be provided.

5.2.3 Protocol Deviations

Important protocol deviation criteria will be established and subjects with important protocol deviations will be identified and documented before the database lock. Also, protocol deviations related to COVID-19 (coronavirus disease 2019) and subjects with the deviations will be identified and documented before database lock.

Subject data listings will be provided.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in Safety Analysis Set.

Continuous demographic and baseline variables include

- Age
- Height
- Weight
- BMI

Categorical demographic and baseline variables include

- Age group (< 65 years, ≥ 65 to < 75 years, ≥ 75 years)
- Weight group (< 60kg, ≥ 60 kg)
- Sex
- Race
- Ethnicity
- ECOG-PS
- NYHA (I, II, III, IV and NA for Heart failure)

Disease history and characteristics at study entry will also be summarized by:

- HCC type (Fibrolamellar, Scirrhous, Spindle cell variant, Pleomorphic type, Clear cell type, Trabecular, Multinodular differentiated, Moderately differentiated, Poorly differentiated, Well differentiated, Biopsy performed – HCC type unknown, Biopsy not performed, Other)
- Child-Pugh score

- BCLC stage
- AFP (as continuous variable)
- AFP group (<200 ng/mL, ≥ 200 ng/mL)
- Macroscopic portal vein invasion (Yes, No)
- Portal vein involvement (Vp0, Vp1, Vp2, Vp3, Vp4)
- Extrahepatic spread (Yes, No)
- Involved disease organ
- Number of involved disease organ per patient (1, 2, ≥3)
- Diagnosis of HCC (Histological or cytological diagnosis of HCC, Clinically confirmed diagnosis of HCC)
- Time from confirmed diagnosis of HCC to the date of first study treatment (months) (as continuous variable)
  - For patients who were "histologically or cytologically" and "clinically" confirmed, whichever earlier diagnosis date is used.
- TNM classification at diagnosis
- Tumor staging at diagnosis
- Factor of Carcinogenesis (Hepatitis B, Hepatitis C, Alcohol, Unknown, Other)
- Number of previous anticancer medication as regimen (0, 1, 2, ≥3)
- Subjects with any previous radiotherapy

Previous anticancer procedure will be summarized by:

- Subjects with any previous anticancer procedure
- Number of previous anticancer procedure (0, 1, 2, 3, 4, ≥5)
- Previous procedure name (Hepatic intra-arterial chemotherapy, Transarterial [chemo] embolization, Radiofrequency ablation, Cryoablation, Percutaneous ethanol injection, Hepatectomy, Other)
- Time from end of most recent procedure to the date of first study treatment (months) (as continuous variable)

Subject data listings will be provided.

Medical History

A subject data listing of medical history and current medical condition will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Prior medications will be defined as medications that started before the first dose of study treatment. Concomitant medications will be defined as medications that (1) started before the first dose

of study treatment and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study treatment up to 30 days after the subject's last dose. Medications received after 30 days of last dose will be considered as post treatment medications.

The number (percentage) of subjects who took prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class (anatomical class, pharmacological class), and WHO DD preferred term on the Safety Analysis Set.

Non-pharmacological procedures will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1 or later).

All medications and non-pharmacological procedures will be presented in subject data listings.

5.2.6 Treatment Compliance

Treatment related protocol deviations will be presented in CSR as provided in the section 5.2.3.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

No adjustment for covariates will be performed.

5.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

5.3.4 Examination of Subgroups

No subgroup analysis will be performed.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

The details of handling of missing data will be described in the section 8.

5.3.6 Other Considerations

Not applicable.

5.4 Efficacy Analyses

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

5.4.1 Efficacy Analyses

Part 1

BOR will be summarized based on mRECIST, and ORR and its 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, following analyses will be performed.

PFS is defined as the time from the date of first dose to the date of first documented PD or death due to any cause (whichever occurs first) and calculated as below. For subjects who do not have an event, PFS will be censored. Censoring rules for PFS are shown in Table 1 Censoring rules for PFS.

PFS (months) = (Date of first documented PD/ death/ censored date – Date of first dose + 1) / (365.25/12).

The PFS rate will be calculated using Kaplan-Meier method. The median, Q1, and Q3 for PFS with their 95% CIs will be evaluated. The 95% CIs will be calculated based on Greenwood formula and a generalized Brookmeyer and Crowley method with log-log transformation. The number (percentage) of subjects with event/censored will be summarized. The PFS rate with its 95% CI at 2, 4, 6, 8, 10 and 12 months will also be calculated, but not limited to these time points. Kaplan-Meier plots with the number of subjects at risk will be presented.

TTP is defined as the time from the date of first dose to the date of first documented PD and calculated as below. For subjects who do not have an event, TTP will be censored. Censoring rules for TTP are shown in Table 2 Censoring rules for TTP. TTP will also be summarized in the same manner as with PFS.

TTP (months) = (Date of first documented PD/ censored date – Date of first dose + 1) / (365.25/12).

DOR is defined as the time from the first documentation of CR or PR to the date of first documented PD or death (whichever occurs first) and calculated as below. DOR will be

calculated only for subjects having at least one CR or PR. Censoring rules for DOR is same as PFS. DOR will also be summarized in the same manner as with PFS.

DOR (months) = (Date of first documented PD/ death/ censored date – Date of the first documentation of CR or PR + 1) / (365.25/12).

TTR is defined as the time from the date of first study dose to the date of first documentation of CR or PR and calculated as below. TTR will be summarized in only subjects with CR or PR using summary statistics.

TTR (months) = (Date of documentation of CR or PR – Date of first dose + 1) / (365.25/12).

OS is defined as the time from the date of first study dose to the date of death due to any cause and calculated as below. 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. Censoring rules for OS are shown in Table 3
Censoring rules for OS. OS will also be summarized in the same manner as with PFS.

OS (months) = (Date of death/ censored date – Date of first dose + 1) / (365.25/12).

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. The diameters after subsequent anti-cancer treatment initiation are not included in the waterfall and spider plot.

Summary statistics for tumor marker (AFP) the changes and percent changes from baseline will be presented by visit. Also, AFP will be categolized as >200 µg/L or <= 200 µg/L and presented by visit.

Subject data listings will be provided.

Table 1 Censoring rules for PFS

No.	Situation	Date of Event or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	Progression documented at scheduled visit	Date of first radiologic PD assessment	Event
3	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
4	No progression nor death at the time of data cut-off or discontinuation from study treatment	Date of last adequate radiologic assessment*	Censored
5	New anticancer treatment started	Date of last adequate radiologic assessment* prior to or on date of new anticancer treatment	Censored
6	Death before first PD assessment	Date of death	Event
7	Death between adequate assessment visits*	Date of death	Event
8	Death or progression after two or more consecutive missed visit/tumor assessment**	Date of last adequate radiologic assessment* before missed tumor assessments	Censored

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than 126 days (ie. 8 weeks x 2 + 2 weeks [allowance of visit]) for subjects on the every 8 week scanning schedule in this study.

The priority of the censoring rules is as follows:
1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of first dose. However, if the subject died within 56 days (8 weeks) after the first dosing date and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
- If a subject had new anticancer treatment before PD or death (No. 5), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more assessments consecutively before PD or death (No. 8), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criteria, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, 3, 6, 7), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, 4, 5, 8).

Table 2 Censoring rules for TTP

No.	Situation	Date of Event or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	Progression documented at scheduled visit	Date of first radiologic PD assessment	Event
3	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
4	No progression at the time of data cut-off or discontinuation from study treatment	Date of last adequate radiologic assessment*	Censored
5	New anticancer treatment started	Date of last adequate radiologic assessment* prior to or on date of new anticancer treatment	Censored
6	Death before first PD assessment	Date of last adequate radiologic assessment*	Censored
7	Death between adequate assessment visits*	Date of last adequate radiologic assessment*	Censored
8	PD after two or more consecutive missed visit/tumor assessment**	Date of last adequate radiologic assessment* before missed tumor assessments	Censored

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined if the duration between the last tumor assessment and PD is longer than 126 days (ie. 8 weeks x 2 + 2 weeks [allowance of visit]) for subjects on the every 8 week scanning schedule in this study.

The priority of the censoring rules is as follows:
1. If the subject had PD, the following sequence will be applied:

- If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of first dose.
- If a subject had new anticancer treatment before PD (No. 5), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more assessments consecutively before PD (No. 8), the subject will be censored on the date of the last adequate tumor assessment before PD.
- Otherwise, if a subject had an event (No. 2, 3), the earliest event date will be used.

2. If a subject did not have PD, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, 4, 5, 6, 7, 8).

Table 3 Censoring rules for OS

No.	Situation	Date of Event or Censoring	Outcome
1	Death before or on data cut off	Date of Death	Event
2	Death after data cut off	Date of data cut off	Censored
3	Subject still alive at data cut off	Date of data cut off	Censored
4	Subject lost to follow-up or withdraw of consent before data cut off	Date last known to be alive	Censored

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual lenvatinib plasma concentrations and nivolumab serum concentrations listings. The PK Analysis Set will be used for the summaries of lenvatinib plasma concentrations and nivolumab serum concentrations, for summaries and listings of PK parameters of lenvatinib. The PK Analysis Set for lenbatinib and for novolumab will be used for each analysis.

5.5.1.1 Plasma or serum Concentration and its PK Parameter Analysis

<Concentration>

Plasma concentration values for lenvatinib and serum concentration values for nivolumab will be summarized by dose level using summary statistics (n, mean, standard deviation [SD], median, minimum [min] and maximum [max]) by Part and nominal time point.

Plasma concentrations of lenvatinib, serum concentrations of nivolumab will be listed for each subject by actual sampling time.

<PK Parameter (Lenvatinib only in Part 1)>

PK parameters will be derived by non-compartmental analysis using WinNonlin software (version 6.2.1 or later) according to 302-104.01-MNL.

The following pharmacokinetic parameters for lenvatinib will be calculated: C_{max} ,t_{max}, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, $t_{½}$, λ_z, CL/F, V_z/F, MRT, $C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, $AUC_{(0\text{-}\tau)}$, CL_{ss}/F, $C_{ss,av}$, $R_{ac}(C_{max})$, R_{ac}(AUC), and PTF ratio.

R_{ac}(AUC) will be calculated based on $AUC_{(0\text{-}t)}$ not $AUC_{(0\text{-}\tau)}$ of Cycle Day1 and Cycle Day 15.

Other PK parameters may be calculated as appropriate.

Summary statistics will be tabulated for the PK parameters of lenvatinib by dose level. Summary statistics (n, mean, SD, median, min, and max) will be presented for all parameters (apart from t_{max} and $t_{ss,max}$ where mean and SD are not required). In addition, geometric mean and %CV will also be presented for all parameters apart from t_{max} and $t_{ss,max}$.

PK parameters of lenvatinib for each subject will be listed.

5.5.1.2 Pharmacokinetic Data Figures

The linear and semi-log plots of plasma concentration for lenvatinib versus actual time will be displayed by individual subjects in Part 1. The actual time will be plotted on the X axis and the concentrations of lenvatinib will be plotted by dose level on the Y axis.The linear and semi-

log mean (+SD) plots of lenvatinib plasma concentration versus nominal time will be displayed in Part 1. The nominal time will be plotted on the X axis and the mean (+SD) will be plotted by dose level on the Y axis on the same graph by visit (Cycle 1 Day 1 and Cycle1 Day 15).

The linear plots of individual and mean (±SD) pre-dose serum concentration for nivolumab will be displayed by Part. For plots of individual concentrations, actual time will be used. For plot of mean concentrations, the nominal time will be used.

The linear mean (±SD) plots of nivolumab pre-dose serum concentration versus nominal time will be displayed by Part. The nominal time will be plotted on the X axis and the mean (±SD) will be plotted on the Y axis.

5.5.2 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. This analysis will be performed only when relavant biomarkers are evaluated and the analysis is deemed nesessary.

5.6 Safety Analyses

All DLT analyses will be performed on the DLT Analysis Set. 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).

5.6.1 Extent of Exposure

The parameters to be summarized are defined as follows.

These parameters for extent of exposure will be computed and presented for lenvatinib alone and nivolumab alone, separately.

For lenvatinib:

- Number of cycles = The last cycle with at least one lenvatinib dosing
- Duration of treatment (days) = Last dosing date – first dosing date + 1
- Duration of treatment (months) = (Last dosing date – first dosing date + 1) / (365.25/12)
- Number of subject-month with study drug dosing = Sum of duration of treatment (months) per subjects
- Total number of doses = Sum of days with lenvatinib dosing
- Total doses (mg) = Sum of all the actual dose
- Dose intensity (mg / days) = Total doses / Duration of treatment (days)
- Relative dose intensity (%) = 100 × Dose intensity / planned starting dose (8 or 12 mg)

For nivolumab:

- Number of cycles = The last cycle with at least one nivolumab dosing
- Duration of treatment (days) = Last dosing date with nivolumab – first dosing date + 1
- Duration of treatment (months) = (Last dosing date with nivolumab – first dosing date + 1) / (365.25/12)
- Number of subject-month with study drug dosing = Sum of duration of treatment (months) per subjects
- Total number of doses = Sum of days with nivolumab dosing
- Total doses (mg) = Sum of all the actual dose derived by [240 (mg) x (Actual volume infused (ml) / volume to be infused (ml))]
- Dose intensity (mg / 2weeks) = Total doses / ((Last dosing date with nivolumab – first dosing date + 14) / 14)
- Relative dose intensity (%) = 100 × Dose intensity / 240 (mg)

Number of cycles as combination therapy of lenvatinib and nivolumab will also be calculated and presented. The smaller number of cycles within a subject is defined as the number of cycle as combination therapy.

Furthermore, the following information of administration will also be summarized for both lenvatinib and nivolumab based on study medication data.

For lenvatinib, the number (percentage) of subjects who experienced a dose reduction and interruption will be summarized. For subjects who experienced a dose reduction, cycle of the first dose reduction will be summarized by descriptive statistics. Cycle of the first dose interruption will also be summarized in subjects who experienced a dose interruption. Frequency of dose reductions will be summarized by categories (1, 2, 3, ≥4). Frequency of dose interruptions will also be summarized by appropriate categories (e.g., 1, 2, 3, ≥4).

The date of dose reduction (from XX mg to YY mg, XX > YY > 0) is defined as the first date of planned dose of 0 mg followed by YY mg. The first date of 0 mg has to follow planned dose of XX mg. If the starting dose of YY mg does not follow 0 mg but XX mg, the first date of planned dose of YY mg is regarded as the date of dose reduction. Note that from 4 mg QD to 4mg QOD is also dose reduction.

The dose interruption is defined as the case where planned dose is 0 mg. The starting date of dose interruption is defined as the first date of planned dose of 0 mg following and followed by same dose level (> 0 mg). For example: 12 mg followed by 0 mg and followed by 12 mg; 8 mg followed by 0 mg followed by 8 mg. Successive days with planned dose of 0 mg is counted as one dose interruption event. If after dose 0 mg, the subject discontinued from lenvatinib permanently, it is not regarded as a drug interruption (but as a drug discontinuation).

An illustration for dose reduction and interruption in a subject is shown in Figure 2.

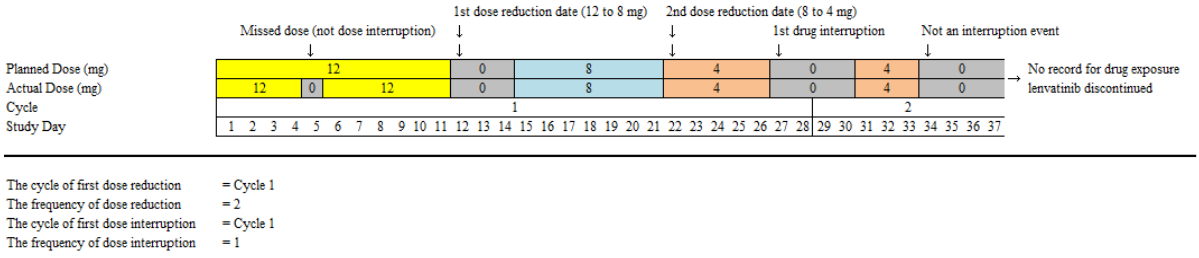


Figure 2 Dose reduction and interruption for lenvatinib

For nivolumab, the number (percentage) of subjects who experienced a dose interruption will be summarized. Cycle of first dose interruption will be summarized by descriptive statistics in subjects who experienced a dose interruption. Frequency of dose interruptions will be summarized by appropriate categories (e.g., 1, 2, 3, ≥4).

The dose interruption is defined as the case where planned dose of 0 mg. Successive dates with planned dose of 0 mg is counted as one dose interruption event, and the first date with

planned dose of 0 mg is defined as the starting date of dose interruption. If after dose 0 mg, the subject discontinued from nivolumab permanently, it is not regarded as a drug interruption (but as a drug discontinuation).

Subject data listings will be provided.

5.6.2 Dose Limiting Toxicity

The number and percentage of subjects with DLT will be calculated. DLT will also be summarized per type of toxicity.

Subject data listings will be provided.

5.6.3 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1 or later). 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) will also be captured in the database.

A treatment-emergent adverse event (TEAE), defined in the section 8.3, will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

An overview table, including the incidence of and the number of subjects with TEAEs, Treatment-related TEAEs, TEAEs with grade 3 or above, serious adverse events (SAEs), deaths, and TEAEs that led to discontinuation of lenvatinib, discontinuation of nivolumab, dose reduction of lenvatinib, dose interruption of lenbatinib and dose interruption of nivolumab will be provided.

The incidence of below events will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT.

- TEAEs (any grade)
- TEAEs by the highest CTCAE grade
- TEAEs grade 3 or above
- Treatment-emergent SAEs
- Non-serious TEAEs
- Treatment-related TEAEs
- Treatment-related TEAEs by the highest CTCAE grade
- Treatment-related TEAEs grade 3 or above
- Treatment-related serious TEAEs

- TEAEs leading to discontinuation of lenvatinib
- TEAEs leading to dose reduction of lenvatinib
- TEAEs leading to dose interruption of lenvatinib
- TEAEs leading to discontinuation of nivolumab
- TEAEs leading to dose interruption of nivolumab

All deaths will also be summarized by primary reasons of deaths (progressive disease, AEs, others), deaths within 30 days of last dose of study drug, deaths >30 days of last dose of study drug, and treatment-related deaths.

Subject data listings of all deaths, SAEs, AEs leading to death, discontinuation of lenvatinib, discontinuation of nivolumab, dose reduction of lenvatinib, dose interruption of lenbatinib and dose interruption of nivolumab will be provided.

Select Adverse Events

The select Adverse Events (select AEs) consist of a list of MedDRA PT grouped by specific category (e.g. endocrine events, and gastrointestinal events categories, etc.). AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. The select AEs and the categories/sub-categories are defined by the Sponsor and the list of PT used for the analyses will be prepared sepalately from SAP.

Select AEs will be summarized by PT on each category/subcategory. The incidence of below events will be reported as the number (percentage) of subjects.

- Select AEs (any grade)
- Select AEs by the highest CTCAE grade
- Select AEs grade 3 or above
- Serious select AEs (any grade)
- Serious select AEs grade 3 or above
- Treatment-related select AEs (any grade)
- Treatment-related select AEs by the highest CTCAE grade
- Treatment-related select AEs grade 3 or above
- Treatment-related serious select AEs (any grade)
- Treatment-related serious select AEs grade 3 or above
- Select AEs leading to discontinuation of nivolumab (any grade)
- Select AEs grade 3 or above leading to discontinuation of nivolumab
- Select AEs leading to dose interruption of nivolumab (any grade)
- Select AEs grade 3 or above leading to dose interruption of nivolumab

Subject data listings of the select AEs will be provided.

5.6.4 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using summary statistics. Qualitative parameters will be summarized by 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.

Box plot display will be used to show the longitudinal change of the parameters by visit.

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

Laboratory parameters will be graded by CTCAE ver. 4.03 in the section 13. Changes from CTCAE grade at baseline to each postbaseline visit and worst postbaseline will be reported using shift tables. CTCAE will also be used to identify subjects with Treatment-emergent markedly abnormal laboratory value (TEMAV). The number (percentage) of subjects with TEMAV (markedly abnormal high/low) will be summarized for each visit and overall study period. The TEMAV will be defined in the section 8.3.

Subject data listings will be provided.

5.6.5 Vital Signs

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

Box plot display will be used to show the longitudinal change of the parameters by visit.

Subject data listings will be provided.

5.6.6 Electrocardiograms

The results of ECG assessments performed at each visit will be evaluated. Summary statistics for ECG parameters (Heart Rate, RR, PR, QRS, QT, and QTcF) and changes from baseline will be presented by visit.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each visit.

In addition, the number (percentage) of subjects who met below criteria at least once in QTcF will be presented:

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

Subject data listings will be provided.

5.6.7 Other Safety Analyses

LVEF

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

Subject data listings will be provided.

ECOG PS

The number (percentage) of subjects for each category of ECOG PS will be summarized by visit. The highest postbaseline scale of ECOG PS for each subject will also be summarized.

Subject data listings will be provided.

5.7 Other Analyses

Immunogenicity

Serum anti-nivolumab antibodies (ADA) will be summarised for subjects which meet all the following criteria.

- Nivolumab is administered once or more.
- It has measurements of ADA (note of, a subject with the sample which baseline result is potential positive but confirmatory result is not available will be excluded) at both baseline and at least one post-treatment anti-drug antibody assessment.

Each sample from the subject is categorized based on the following definitions:

Sample ADA Status:

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment
- Baseline ADA-negative sample: ADA is not detected in the last sample before initiation of treatment
- ADA-positive sample: After initiation of treatment, (1) an ADA detected (positive

seroconversion) sample in a subject for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least 4-fold or greater (≥) than baseline positive titer
- ADA-negative sample: After initiation of treatment, ADA not positive sample relative to baseline (except missing data).

Next, using the sample ADA status, subject ADA status is defined as follows:

Subject ADA Status:

- Baseline ADA-positive subject: A subject with baseline ADA-positive sample. Among the baseline ADA-positive subjects, the subject who has baseline ADA-positive sample with neutralizing antibodies detected will be defined as the baseline neutralizing positive.
- ADA-positive subject: A subject with at least one ADA positive-sample relative to baseline at any time after initiation of treatment
  1) Persistent Positive (PP): ADA-positive sample at 2 or more consecutive time points, where the first and last ADA-positive samples are at least 15 weeks apart
  2) Not PP-Last Sample Positive: Not persistent positive with ADA-positive sample at the last sampling time point
  3) Other Positive: Not persistent positive but some ADA-positive samples with the last sample being negative
  4) Neutralizing Positive: At least one ADA-positive sample with neutralizing antibodies detected
- ADA-negative subject: A subject with no ADA-positive sample after the initiation of treatment.

The number (percentage) of subjects will be summarized by part for the following subject ADA status.

- Baseline ADA-positive
- ADA-positive
  - Persistent Positive (PP)
  - Not PP-Last Sample Positive
  - Other Positive
- ADA-negative

Subject data listing of all ADA assessments will be provided.

For exploratory purpose, the number (percentage) of subject with the baseline neutralizing positive/neutralizing positive may be summarized, if appropriate. Also, subject data listings of ADA assessments for subjects with neutralizing positive may be provided.

5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

6 INTERIM ANALYSES

No interim analysis will be conducted.

7 CHANGES IN THE PLANNED ANALYSES

A summary of all major additions, changes and deletions in the planned analyses described in the protocol will be provided in this section.

[redacted]

- Definition of PK Analysis Set was changed to set for PK Analysis Set for Lenvatinib and PK Analysis Set for Nivolumab separately.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

8.1 General Data Handling

Definition of Baseline data

Baseline is defined as the last non-missing value observed prior to the first dose of study treatment for a given parameter.

Definition of Change from Baseline, Percent Change from Baseline

Change from baseline is defined as post-baseline value minus baseline value.
Percent change from baseline is defined as follows:

% Change from baseline = (Change from baseline / Baseline) * 100%

For any Baseline value of 0, the subject's corresponding percent change from baseline will not be included in the summary statistics table.

8.2 Efficacy Data Handling

Handling of missing data for tumor assessment result

For the analysis of ORR, DCR and CBR, subjects with missing response status (subjects whose baseline is missing and/or no adequate post-baseline tumor assessments result) will be coded as non-responders on Efficacy Analysis Set.

Data of tumor assessment result after documented PD or discontinuation from treatment

For the analysis of tumor assessment relevant efficacy endpoints, tumor assessment result after PD or final observation visit (for non-PD patients) are excluded from the analyses, but included in subject data listing.

Visit Windows

The purpose of visit windows is to provide a single record per subject per visit for the calculation of descriptive statistics for tumor marker per scheduled visit, and change from baseline per visit.

The observation closest to the target date will be used in by visit summaries. If two or more observations have the same distance to the target visit day, the one that has the highest value will be used for summary tables. If the multiple data in the same distance to the target date are same, the data measured at an earlier date will be used for summary tables.

The visit window is applied for tumor marker assessment summary.

Analysis visit	Target Day	Analysis Window	
		Start Day	End Day
Cycle 3 Day 1	Cycle 3 Day 1	Cycle 3 Day 1 - 7	Cycle 3 Day 1 + 7
Cycle 5 Day 1	Cycle 5 Day 1	Cycle 5 Day 1 - 7	Cycle 5 Day 1 + 7
Cycle n Day 1 (n ≥ 7 and odd numbers)	Cycle n Day 1	Cycle n Day 1 - 7	Cycle n Day 1 + 7

8.3 Safety Data Handling

Treatment-emergent adverse event

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

- Reemerged during treatment, having been present at pretreatment but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

Adverse Events

Adverse Events with incomplete start dates will be considered treatment emergent if:

a. Day and month are missing and the year is equal to or after the year of the first dose date;

b. Day is missing, and the year is after the year of the first dose;

c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;

d. Year is missing;

e. Complete date is missing.

Concomitant Medications

Medications with incomplete end dates will be considered concomitant if:

a. Day and month are missing and the year is equal to or after the year of the first dose date;

b. Day is missing, and the year is after the year of the first dose;

c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date; or

d. Year is missing;

e. Complete date is missing.

OR; complete end dates is between the date of first study dose and date of last study dose even if the start date of medications is incomplete.

TEMAV (Treatment-Emergent Markedly Abnormal Value)

Treatment-emergent markedly abnormal laboratory value (TEMAV) is defined as a postbaseline laboratory value with grade 3 or higher, and with a grade increase from baseline. (ie., Increasing grade 0 to 3 or higher, grade 1 to 3 or higher, grade 2 to 3 or higher, grade 3 to 4 or 5, grade 4 to 5.)

Handling of below lower quantification values in laboratory results

In the cases where laboratory result contains below lower quantification (BLQ) value, it will be replaced to the lower limit value of quantification (LLOQ) for summary tables.

The priority of use for blood pressure

For systolic and diastolic blood pressures, additional confirmatory assessment will be done more than 60 minutes after initial assessment, if necessary. In the case where there are both the initial and confirmatory assessment results in a day, confirmatory one will be used.

Calculation of creatinine clearance

To calculate a creatinine clearance (mL/min), the Cockcroft & Cault formula will be used.

Males: ((140 – age (years)) × weight (kg)) / (Creatinine (serum:mg/dL) × 72)

Females: ((140 – age (years)) × weight (kg) ×0.85) / (Creatinine (serum:mg/dL) × 72)

Visit Windows

The purpose of visit windows is to provide a single record per subject per visit for the calculation of descriptive statistics for safety parameters (e.g., laboratory values and vital signs, etc.) per scheduled visit, and change from baseline per visit. Other safety analyses (e.g., worst grade laboratory results) will include all observations.

The observation closest to the target date will be used in by visit summaries. If two or more observations have the same distance to the target visit day, the one that has the highest CTCAE grade or is furthest away from the normal range will be used for summary tables. If

the multiple data in the same distance to the target date are in the same range from normal value, the data measured at an earlier date will be used for summary tables.

The visit window is applied for safety assessment item which is scheduled at each visit.

Analysis visit	Target Day	Visit Window	
		Start Day of Visit Window	End Day of Visit Window
Cycle 1 Day 8	Cycle 1 Day 1 + 7	Cycle 1 Day 1 + 5	Cycle 1 Day 1 + 9
Cycle 1 Day 15	Cycle 1 Day 1 + 14	Cycle 1 Day 1 + 12	Cycle 1 Day 1 + 16
Cycle 1 Day 22	Cycle 1 Day 1 + 21	Cycle 1 Day 1 + 19	Cycle 1 Day 1 + 23
Cycle 2 Day 1	Cycle 1 Day 1 + 28	Cycle 1 Day 1 + 28	Cycle 1 Day 1 + 31
Cycle 2 Day 8	Cycle 1 Day 1 + 35	Cycle 1 Day 1 + 32	Cycle 1 Day 1 + 38
Cycle 2 Day 15	Cycle 1 Day 1 + 42	Cycle 1 Day 1 + 39	Cycle 1 Day 1 + 45
Cycle 2 Day 22	Cycle 1 Day 1 + 49	Cycle 1 Day 1 + 46	Cycle 1 Day 1 + 52
Cycle n Day 1 (n ≥ 3)	Cycle 1 Day 1 + 28 x (n-1)	Cycle 1 Day 1 + 28 x (n-1) - 3	Cycle 1 Day 1 + 28 x (n-1) + 3
Cycle n Day 8 (n ≥ 3)	Cycle 1 Day 1 + 28 x (n-1) + 7	Cycle 1 Day 1 + 28 x (n-1) + 4	Cycle 1 Day 1 + 28 x (n-1) + 10
Cycle n Day 15 (n ≥ 3)	Cycle 1 Day 1 + 28 x (n-1) + 14	Cycle 1 Day 1 + 28 x (n-1) + 11	Cycle 1 Day 1 + 28 x (n-1) + 17
Cycle n Day 22 (n ≥ 3)	Cycle 1 Day 1 + 28 x (n-1) + 21	Cycle 1 Day 1 + 28 x (n-1) + 18	Cycle 1 Day 1 + 28 x (n-1) + 24
End of Treatment	30 days after last dose	Date of last dose	Date of last dose + 37

C1D1 is the day of first dosing.

8.4 Pharmacokinetic Data Handling

8.4.1 Lower Limit of Quantification of lenvatinib Plasma Concentration and Nivolumab Serum Concentration

The LLOQ of lenvatinib plasma concentrations is 0.100 ng/mL

The LLOQ of nivolumab serum concentrations is 0.200 μg/mL

8.4.2 BLQ Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, BLQ values will be handled according to 302-104.01-MNL, for non-compartmental pharmacokinetic analysis.

8.4.3 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.01-MNL for non-compartmental pharmacokinetic analysis.

8.4.4 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the SWP for non-compartmental pharmacokinetic analysis (302-104.01-MNL).

8.4.5 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD and coefficient variation (CV)) will have 3 significant digits. For t_{max} and $t_{ss,max}$, raw values and their median are shown in fixed 2 decimal places.

Variable	Unit	N	Digit rule	Raw/ Minimum/ Maximum	Mean Median	SD	Geometric Mean	CV (%)
drug concentration	ng/mL	X	Significant digits	3	3	3	-	-
C_{max}, $C_{ss,max}$, C_{min}, $C_{ss,av}$	ng/mL	X	Significant digits	3	3	3	3	3
t_{max}, $t_{ss,max}$	h	X	Fixed decimal places	2	2	-	-	-
λ_z(C1D1&D15)	1/h	X	Significant digits	3 (Listing only)	-	-	-	-
$t_{1/2}$(C1D1&D15)	h	X	Significant digits	3	3	3	3	3
$AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-ti)}$, $AUC_{(0-\tau)}$	ng•h/mL	X	Significant digits	3	3	3	3	3
CL/F, CL_{ss}/F	L/h	X	Significant digits	3	3	3	3	3
V_z/F(C1D1&D15)	L	X	Significant digits	3	3	3	3	3
R_{ac}		X	Significant digits	3	3	3	3	3
PTF ratio	%	X	Significant digits	3	3	3	3	3

Mean, SD, geometric mean and CV will not be calculated for t_{max}, $t_{ss,max}$.

CV(%)= sqrt(exp[SD**2 of log transformed data]-1)*100

NOTE

1. The following parameters are reported in the CSR, but appear in Listings only. They are important information to confirm that individual $t_{1/2}$ and its related parameters such as$AUC_{(0-inf)}$ are appropriately derived and allow those PK parameters to be reproduced when necessary.
   a. Time points used for estimation of λ_z (lower and upper)
   b. Number of the time points used for λ_z
   c. Adjusted regression coefficient (R_{2adj})
   d. Percentage of $AUC_{(0-inf)}$ obtained by extrapolation ($\%AUC_{ex}$)
   e. The last time points used for calculation of $AUC_{(0-t)}$ (t_{last})

In Listings, a) and e) are shown in same digits as actual sampling time after dosing used for calculation of PK parameters. For b), integer number is used in Listings. For c) and d), significant 3 digits are used in Listing.

8.4.6 Handling of Individual Data

The following cases will be excluded for the calculation of summary statistics.

- Blood samples at predose are collected after administration
- Overdose
- Blood samples for nivolumab PK assessment are collected when the most recent dosing of nivolumab is interrupted.
- Blood samples for lenvatinib PK assessment are collected when the most recent dosing of lenvatinib is reduced or interrupted.
- Regarding lenvatinib PK assessment from Cycle 1 Day 1 to Cycle 1 Day 16 in Part 1, blood samples for lenvatinib PK assessment are collected after dose reduction or interruption of lenvatinib by Cycle 1 Day 15.
- Dosing and/or sampling date/time are missing
- Blood samples are not taken in the nominal time point
- Concentration data collected at Discontinuation or Off-Treatment visit.

The following case will be determined individually.

- Significant deviation from the allowance of PK blood sampling schedule. However, concentration data at predose will not be excluded when the blood sampling is collected at predose on the scheduled day.
- There is discrepancy between planned and actual volume of nivolumab dosing.
- Concentration data is not scientifically valid (e.g, concentration at predose on Cycle 1 Day 1 is not BLQ and concentration at just completion of dosing is BLQ.)

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be conducted by Takumi Information Technology, using validated standard programs or double programming. For analyses needed in data review, single programming will be used.

All statistical analyses will be performed using SAS (version 9.3 or later). As necessary, other validated statistical software will also be used.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

- FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Dec 2018 [internet; cited on 3rd Apr 2023] Available from: https://www.fda.gov/media/71195/download

13 APPENDICES

13.1 National Institute for Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

National Cancer Institute (NCI) Cancer therapy evaluation program Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 May 2009 (v4.03 June 2010) is available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

CTCAE grades for selected laboratory parameters are listed in the table below, where ULN is the upper limit of normal and LLN is the lower limit of normal.

Lab Parameter	**NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units**				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hematology					
Hemoglobin (low)	100 - <LLN (g/L)	80 - <100 (g/L)	<80 (g/L)	__	Death
Hemoglobin (high)	Increase in >0 - 20 g/L above ULN (ie.., Increase in >0 - 2 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >20 - 40 g/L above ULN (ie.., Increase in >2 - 4 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >40 g/L above ULN (ie.., Increase in >4 gm/dL above ULN) or above baseline if baseline is above ULN	__	__
Platelet Count (PLT) (low)	75 - <LLN (x 10^9/L)	50 - <75 (x 10^9/L)	25 - <50 (x 10^9/L)	<25 (x 10^9/L)	__
White Blood Cell Count (WBC) (low)	3 - <LLN (x 10^9/L)	2 - <3 (x 10^9/L)	1 - <2 (x 10^9/L)	<1 (x 10^9/L)	__
White Blood Cell Count (WBC) (high)	__	__	>100 x 10^9/L (ie.., >100,000/mm^3)	__	Death
Lymphocytes (low)	0.8 - <LLN (x 10^9/L)	0.5 - <0.8 (x 10^9/L)	0.2 - <0.5 (x 10^9/L)	<0.2 (x 10^9/L)	__
Lymphocytes (high)	__	>4 - 20 (x 10^9/L) (ie.., >4,000 - 20,000/mm^3)	>20 (x 10^9/L) (ie.., > 20,000/mm^3)	__	__
Neutrophils (low)	1.5 - <LLN (x 10^9/L)	1 - <1.5 (x 10^9/L)	0.5 - <1 (x 10^9/L)	<0.5 (x 10^9/L)	__

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blood Coagulation					
INR (high)	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	__	__
Blood Chemistry					
Albumin (low)	30 - <LLN (g/L)	20 - <30 (g/L)	<20 (g/L)	__	Death
Alkaline Phosphatase (ALP) (high)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
ALT (SGPT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
AST (SGOT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
Total Bilirubin (high)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	__
Calcium, serum-low (hypocalcemia)	2.0 - <LLN (mmol/L) (ie.., 8.0 mg/dL - <LLN) *	1.75 - <2 (mmol/L) (ie.., 7.0 - <8.0 mg/dL) *	1.5 - <1.75 (mmol/L) (ie.., 6.0 - <7.0 mg/dL) *	<1.5 (mmol/L) (ie.., <6.0 mg/dL) *	Death
Calcium, serum-high (hypercalcemia)	>ULN – 2.9 (mmol/L) (ie.., >ULN – 11.5 mg/dL) *	>2.9 – 3.1 (mmol/L) (ie.., >11.5 – 12.5 mg/dL) *	>3.1 – 3.4 (mmol/L) (ie.., >12.5 – 13.5 mg/dL) *	>3.4 (mmol/L) (ie.., >13.5 mg/dL) *	Death
Cholesterol (high)	>ULN -7.75 mmol/L	>7.75 -10.34 mmol/L	>10.34 -12.92 mmol/L	>12.92 mmol/L	__
CPK (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	__
Creatinine (high)	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN	>6.0 x ULN	__
GGT (gamma-glutamyltransferase) (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5.0 x ULN	>5.0 x ULN – 20.0 x ULN	>20.0 x ULN	__
Glucose, serum-low (hypoglycemia)	3 - <LLN (mmol/L)	2.2 - <3 (mmol/L)	1.7 - <2.2 (mmol/L)	<1.7 (mmol/L)	Death

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Glucose, serum-high (hyperglycemia)	ULN – 8.9 (mmol/L)	>8.9 – 13.9 (mmol/L)	>13.9 – 27.8 (mmol/L)	>27.8 (mmol/L)	Death
Lipase (high)	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	__
Magnesium (low)	<LLN – 0.5 (mmol/L)	<0.5 – 0.4 (mmol/L)	<0.4 – 0.3 (mmol/L)	<0.3 (mmol/L)	Death
Magnesium (high)	>ULN – 1.23 (mmol/L)	__	>1.23 – 3.30 (mmol/L)	>3.30 (mmol/L)	Death
Triglyceride (hypertriglyceridemia) (high)	1.71 – 3.42 (mmol/L)	>3.42 – 5.7 (mmol/L)	>5.7 – 11.4 (mmol/L)	>11.4 (mmol/L)	Death
Phosphate, serum-low (hypophosphatemia)	0.8 - <LLN (mmol/L)	0.6 - <0.8 (mmol/L)	0.3 - <0.6 (mmol/L)	<0.3 (mmol/L)	Death
Potassium, serum-low (hypokalemia)	3.0 - <LLN (mmol/L)	__	2.5 - <3.0 (mmol/L)	<2.5 (mmol/L)	Death
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 (mmol/L)	>5.5 – 6.0 (mmol/L)	>6.0 – 7.0 (mmol/L)	>7.0 (mmol/L)	Death
Uric Acid (hyperuricemia) (high)	>ULN – 590 (umol/L)	__	__	>590 (umol/L)	__
Sodium, serum-low (hyponatremia)	130 - <LLN (mmol/L)	__	120 - <130 (mmol/L)	<120 (mmol/L)	Death
Sodium, serum-high (hypernatremia)	>ULN - 150 (mmol/L)	>150 - 155 (mmol/L)	>155 - 160 (mmol/L)	>160 (mmol/L)	Death
Urinalysis					

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Proteinuria (high)	1+ proteinuria; urinary protein <1.0 g/24 hrs	≥2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs	urinary protein >=3.5 g/24 hrs	__	__

* Corrected serum calcium by albumin should be referred. If serum albumin is <4.0 g/dL, the corrected calcium will be calculated using the following formula: Corrected calcium (mg/dL) = Total calcium (mg/dL) – 0.8 x [Albumin (g/dL) – 4]

SIGNATURE PAGE

Author:

Electlonic signature in eDMS

PPD
PPD
DHBL

Date

Approval:

Electlonic signature in eDMS

PPD PPD
PPD
PPD
DHBL

Date

Electlonic signature in eDMS

Study Director

PPD
PPD
DHBL

Date

Electlonic signature in eDMS

Pharmacokinetic Analyst

PPD
PPD
DHBL

Date

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7080-J081-117
Study Protocol Title:	A Phase 1b Trial of Lenvatinib Plus Nivolumab in Subjects with Hepatocellular Carcinoma
Date:	17 Jan 2018
Version:	Version 1.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
AFP	α-fetoprotein
ATC	anatomical therapeutic chemical
BCLC	Barcelona Clinic Liver Cancer
BLQ	below lower quantification
BMI	body mass index
BOR	best overall response
BW	body weight
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	common toxicity criteria for adverse events
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HCC	hepatocellular carcinoma
IV	Intravenous
LLOQ	lower limit of quantification
LLT	lower level term
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multiple-gated acquisition technique
NE	not evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PD	progressive disease

Abbreviation	Term
PFS	progression free survival
PGx	pharmacogenomics
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
QD	every day
QOD	every other day
QTcF	QT interval corrected for heart rate using Fridericia's formula
Q2W	every 2 weeks
RECIST	response evaluation criteria in solid tumor
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SD	standard deviation
SI	système international
SOC	system organ class
SpO_2	percutaneous oxygen saturation
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TLG	tables, listings, and graphs
TNM	tumor, nodes, metastasis
TTP	time to progression
TTR	time to response
WHO DD	World Health Organization drug dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E7080-J081-117.

3.1 Study Objectives

3.1.1 Primary Objective

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

3.1.2 Secondary Objectives

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

3.1.3 Exploratory Objective

3.2 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 HCC for which no other appropriate therapy

is available. Part 2 is to further characterize the safety and tolerability and to assess preliminary efficacy of the combination therapy in HCC with no prior systemic therapy.

3.2.1 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 is 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])

The tolerability will be reviewed based on Dose Limiting Toxicity (DLT) of Cycle 1 (4 weeks) according to the following procedures.

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 investigators.

(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.

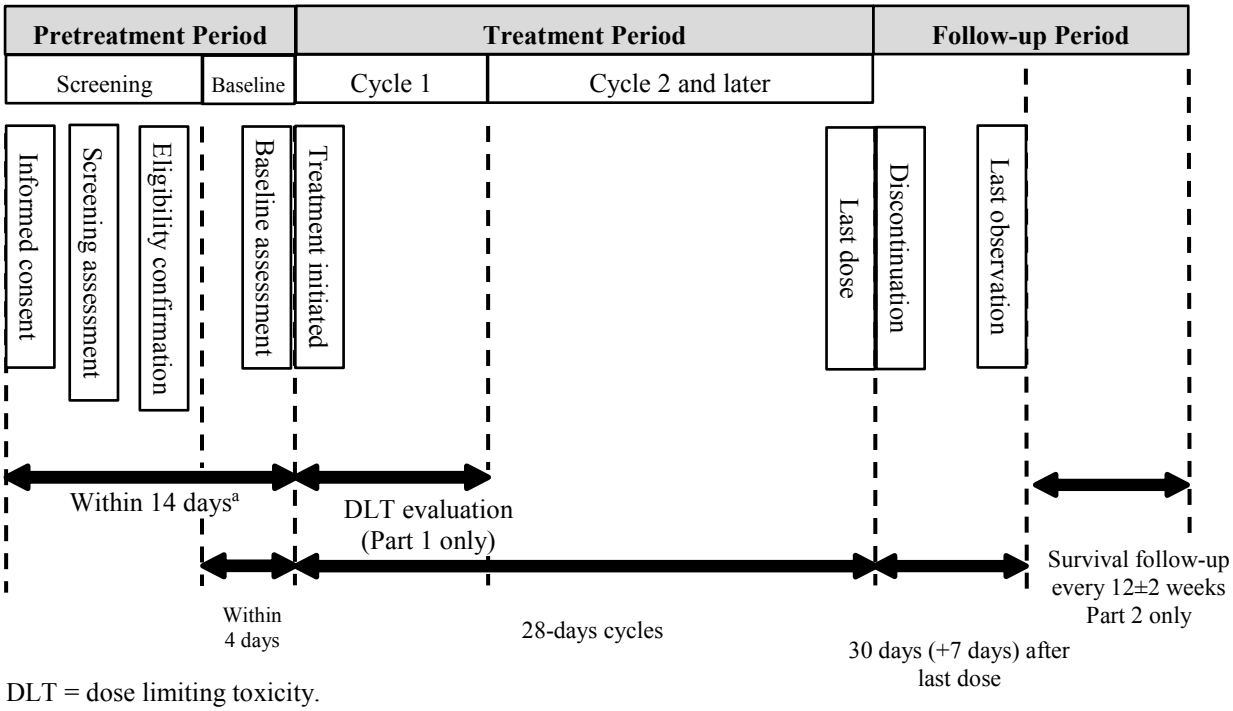
In this dose level, at least 3 subjects treated with lenvatinib 12 mg (BW ≥60 kg) and nivolumab need to be included in the 6 subjects for DLT evaluation. If this dose level is not tolerable, upon discussions between the sponsor, sponsor's responsible medical officer, and investigators, the lower dose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

3.2.2 Part 2

If the dose level is confirmed to be tolerable, 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.

3.2.3 Study Design

An overview of the study design is presented in Figure 1. Part 1 and Part 2 will consist of a pretreatment period, a treatment period, and a follow-up period.



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.)

Figure 1 Study Design

3.2.3.1 Pretreatment Period

The pretreatment period 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 Period.

3.2.3.2 Treatment Period

In the Treatment Period, subjects will receive lenvatinib in combination with nivolumab. The Treatment Period will begin with the first dose of study drug administration on Cycle 1

Day 1. Each cycle is 28 days long and subjects continue treatment until they meet any of the criteria in "Discontinuation Criteria by Subject (see Protocol Section 9.3.3.1)".

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

3.2.3.3 Follow-up Period

The follow-up period will consist of the examination at study discontinuation and the last observation visit which occurs 30 days after final administration of study drug. If the last observation visit occurs within 7 days after study drug discontinuation, discontinuation data can be used as the last observation data. 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 the new anticancer agent.

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.

4 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.

5 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the data cutoff for 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.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

All statistical analysis will be performed by part separately. Summarization for lenvatinib 8 mg group, 12 mg group and total subjects will be presented.

5.1 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.

5.1.1 Primary Endpoints

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

5.1.2 Secondary Endpoints

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

5.1.2.1 Pharmacokinetic (PK) Endpoints

PK parameters derived by non-compartmental analysis using plasma concentrations of lenvatinib which include, but are not limited to, are shown as below:

C_{max}	maximum observed concentration
t_{max}	time at which the highest drug concentration occurs
$AUC_{(0-t)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
$AUC_{(0-ti)}$	area under the concentration-time curve from zero (pre-dose) to a given sampling time (ti)
$AUC_{(0-inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$t_{½}$	terminal elimination phase half-life

CL/F	apparent total clearance following oral dosing
V_z/F	apparent volume of distribution at terminal phase
$C_{ss,max}$	maximum observed concentration at steady state
$C_{ss,min}$	minimum observed concentration at steady state
$t_{ss,max}$	time at which the highest drug concentration occurs at steady state
$AUC_{(0-\tau)}$	area under the concentration-time curve over the dosing interval
CL_{ss}/F	apparent total clearance following oral administration at steady state
$C_{ss,av}$	average steady-state concentration
$R_{ac}(C_{max})$, $R_{ac}(AUC)$	accumulation index
PTF ratio	peak-trough fluctuation ratio

5.1.3 Exploratory Endpoints

CCI

progression or death, whichever occurs first. For censored subjects before documentation of disease progression or death, duration of SD is defined as the time from the first study dose date to the censored date. The censoring rule is same as PFS. The duration of SD is used to define durable SD and it is calculated in patients whose BOR was SD.

5.2 Study Subjects

5.2.1 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.

The number of subjects enrolled, the number (percentage) of subjects included in each analysis set will be presented. Subject data listings will be provided.

5.2.2 Subject Disposition

For the summary table of screening subjects, the number (percentage) of subjects who were enrolled (ie, subjects who signed informed consent), continued in the study after screening, failed screening, and the primary reason for screen failures will be presented.

For the summary of the subject disposition, the number (percentage) of subjects who were treated/not treated, completed/discontinued the study, and the reason for the study discontinuation will be presented. Similarly, the number (percentage) of subjects who completed/discontinued the study treatment, and the reason for the discontinuation from study treatment will also be summarized. The number (percentage) of subjects who discontinued either lenvatinib alone or nivolumab alone and the reason for discontinuation will be summarized.

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.

Subject data listings will be provided.

5.2.3 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock. The protocol deviations identified according to the criteria at study entry and during treatment will not be included in TLGs covered by SAP, but will be presented in the clinical study report (CSR).

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in Safety Analysis Set.

Continuous demographic and baseline variables include

- Age
- Height
- Weight
- BMI

Categorical demographic and baseline variables include

- Age group (< 65 years, ≥ 65 to < 75 years, ≥ 75 years)
- Weight group (< 60kg, ≥ 60 kg)
- Sex
- Race
- Ethnicity
- ECOG-PS
- NYHA (I, II, III, IV and NA for Heart failure)

Disease history and characteristics at study entry will also be summarized by:

- HCC type (Fibrolamellar, Scirrhous, Spindle cell variant, Pleomorphic type, Clear cell type, Trabecular, Multinodular differentiated, Moderately differentiated, Poorly differentiated, Well differentiated, Biopsy performed – HCC type unknown, Biopsy not performed, Other)
- Child-Pugh score
- BCLC stage
- AFP (as continuous variable)
- AFP group (<200 ng/mL, ≥ 200 ng/mL)

- Macroscopic portal vein invasion (Yes, No)
- Portal vein involvement (Vp0, Vp1, Vp2, Vp3, Vp4)
- Extrahepatic spread (Yes, No)
- Involved disease organ
- Number of involved disease organ per patient (1, 2, ≥3)
- Diagnosis of HCC (Histological or cytological diagnosis of HCC, Clinically confirmed diagnosis of HCC)
- Time from confirmed diagnosis of HCC to the date of first study treatment (months) (as continuous variable)
  - For patients who were "histologically or cytologically" and "clinically" confirmed, whichever earlier diagnosis date is used.
- TNM classification at diagnosis
- Tumor staging at diagnosis
- Factor of Carcinogenesis (Hepatitis B, Hepatitis C, Alcohol, Unknown, Other)
- Number of previous anticancer medication as regimen (0, 1, 2, ≥3)
- Subjects with any previous radiotherapy

Previous anticancer procedure will be summarized by:

- Subjects with any previous anticancer procedure
- Number of previous anticancer procedure (0, 1, 2, 3, 4, ≥5)
- Previous procedure name (Hepatic intra-arterial chemotherapy, Transarterial [chemo] embolization, Radiofrequency ablation, Cryoablation, Percutaneous ethanol injection, Hepatectomy, Other)
- Time from end of most recent procedure to the date of first study treatment (months) (as continuous variable)

Subject data listings will be provided.

Medical History

A subject data listing of medical history and current medical condition will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Prior medications will be defined as medications that stopped before the first dose of study treatment. Concomitant medications will be defined as medications that (1) started before the first dose of study treatment and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study treatment up to 30 days after

the subject's last dose. Medications received after 30 days of last dose will be considered as post treatment medications.

The number (percentage) of subjects who took prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class (anatomical class, pharmacological class), and WHO DD preferred term on the Safety Analysis Set.

Non-pharmacological procedures will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1 or later).

All medications and non-pharmacological procedures will be presented in subject data listings.

5.2.6 Treatment Compliance

Treatment related protocol deviations will be presented in CSR as provided in the section 5.2.3.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

No adjustment for covariates will be performed.

5.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

5.3.4 Examination of Subgroups

The subgroup analyses will be performed, if deemed appropriate. The definition of subgroup will be determined and documented in SAP before database locked.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

The details of handling of missing data will be described in the section 8.

5.3.6 Other Considerations

Not applicable.

5.4 Efficacy Analyses

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

5.4.1 Efficacy Analyses

Part 1

BOR will be summarized based on mRECIST, and ORR and its 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, following analyses will be performed.

PFS is defined as the time from the date of first dose to the date of first documented PD or death due to any cause (whichever occurs first) and calculated as below. For subjects who do not have an event, PFS will be censored. Censoring rules for PFS are shown in Table 1.

PFS (months) = (Date of first documented PD/ death/ censored date – Date of first dose + 1) / (365.25/12).

The cumulative PFS rate will be calculated using Kaplan-Meier method. The median, Q1, and Q3 for PFS with their 95% CIs will be evaluated. The 95% CIs will be calculated based on Greenwood formula and log-log transformation. The number (percentage) of subjects with event/censored will be summarized. The PFS rate with its 95% CI at 2, 4, 6, 8, 10 and 12 months will also be calculated, but not limited to these time points. Kaplan-Meier plots with the number of subjects at risk will be presented.

TTP is defined as the time from the date of first dose to the date of first documented PD and calculated as below. For subjects who do not have an event, TTP will be censored. Censoring rules for TTP are shown in Table 2. TTP will also be summarized in the same manner as with PFS.

TTP (months) = (Date of first documented PD/ censored date – Date of first dose + 1) / (365.25/12).

DOR is defined as the time from the first documentation of CR or PR to the date of first documented PD or death (whichever occurs first) and calculated as below. DOR will be calculated only for subjects having at least one CR or PR. Censoring rules for DOR is same as PFS.

DOR (months) = (Date of first documented PD/ death/ censored date – Date of the first documentation of CR or PR + 1) / (365.25/12).

TTR is defined as the time from the date of first study dose to the date of first documentation of CR or PR and calculated as below. TTR will be summarized in two populations (1) all subjects (2) only subjects having event. For subjects who do not have an event, TTR will be censored. Censoring rules for TTR are shown in Table 3. TTR will also be summarized in the same manner as with PFS, but the Kaplan-Meier plot will be described in bottom-up style and corresponding rates at each time point will be presented.

TTR (months) = (Date of documentation of CR or PR / censored date – Date of first dose + 1) / (365.25/12).

OS is defined as the time from the date of first study dose to the date of death due to any cause and calculated as below. 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. Censoring rules for OS are shown in Table 4. OS will also be summarized in the same manner as with PFS.

OS (months) = (Date of death/ censored date – Date of first dose + 1) / (365.25/12).

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. The diameters after subsequent anti-cancer treatment initiation are not included in the waterfall and spider plot.

Summary statistics for tumor marker (AFP) the changes and percent changes from baseline will be presented by visit.

Subject data listings will be provided.

Table 1 Censoring rules for PFS

No.	Situation	Date of Event or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	Progression documented at scheduled visit	Date of first radiologic PD assessment	Event
3	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
4	No progression nor death at the time of data cut-off or discontinuation from study treatment	Date of last adequate radiologic assessment*	Censored
5	New anticancer treatment started	Date of last adequate radiologic assessment* prior to or on date of new anticancer treatment	Censored
6	Death before first PD assessment	Date of death	Event
7	Death between adequate assessment visits*	Date of death	Event
8	Death or progression after two or more consecutive missed visit/tumor assessment**	Date of last adequate radiologic assessment* before missed tumor assessments	Censored

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than 126 days (ie. 8 weeks x 2 + 2 weeks [allowance of visit]) for subjects on the every 8 week scanning schedule in this study.

The priority of the censoring rules is as follows:
1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of first dose. However, if the subject died within 56 days (8 weeks) after the first dosing date and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
- If a subject had new anticancer treatment before PD or death (No. 5), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more assessments consecutively before PD or death (No. 8), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criteria, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, 3, 6, 7), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, 4, 5, 8).

Table 2 Censoring rules for TTP

No.	Situation	Date of Event or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	Progression documented at scheduled visit	Date of first radiologic PD assessment	Event
3	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
4	No progression at the time of data cut-off or discontinuation from study treatment	Date of last adequate radiologic assessment*	Censored
5	New anticancer treatment started	Date of last adequate radiologic assessment* prior to or on date of new anticancer treatment	Censored
6	Death before first PD assessment	Date of last adequate radiologic assessment*	Censored
7	Death between adequate assessment visits*	Date of last adequate radiologic assessment*	Censored
8	PD after two or more consecutive missed visit/tumor assessment**	Date of last adequate radiologic assessment* before missed tumor assessments	Censored

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined if the duration between the last tumor assessment and PD is longer than 126 days (ie. 8 weeks x 2 + 2 weeks [allowance of visit]) for subjects on the every 8 week scanning schedule in this study.

The priority of the censoring rules is as follows:
1. If the subject had PD, the following sequence will be applied:

- If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of first dose.
- If a subject had new anticancer treatment before PD (No. 5), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more assessments consecutively before PD (No. 8), the subject will be censored on the date of the last adequate tumor assessment before PD.
- Otherwise, if a subject had an event (No. 2, 3), the earliest event date will be used.

2. If a subject did not have PD, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, 4, 5, 6, 7, 8).

Table 3 Censoring rules for TTR

No.	Situation	Date of Event or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	CR or PR documented at scheduled visit	Date of first CR or PR assessment	Event
3	CR or PR documented between scheduled visits	Date of first CR or PR assessment	Event
4	No CR nor PR by the time of data cut-off or discontinuation from study treatment	Date of last adequate radiologic assessment*	Censored
5	New anticancer treatment started	Date of last adequate radiologic assessment* prior to or on date of new anticancer treatment	Censored
6	Death before first CR or PR assessment	Date of last adequate radiologic assessment*	Censored
7	Death between adequate assessment visits*	Date of last adequate radiologic assessment*	Censored
8	CR or PR after two or more consecutive missed visit/tumor assessment**	Date of first CR or PR assessment	Event

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined if the duration between the last tumor assessment and CR or PR is longer than 126 days (ie. 8 weeks x 2 + 2 weeks [allowance of visit]) for subjects on the every 8 week scanning schedule in this study.

The priority of the censoring rules is as follows:
1. If the subject had CR or PR, the following sequence will be applied:

- If a subject had new anticancer treatment before CR or PR (No. 5), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- Otherwise, if a subject had an event (No. 2, 3, 8), the earliest event date will be used. Even if a subject missed two or more assessments consecutively before CR or PR (No. 8), the subject will be counted as event case on the date of the tumor assessment with CR or PR.

2. If a subject did not have CR or PR, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, 4, 5, 6, 7).

Table 4 Censoring rules for OS

No.	Situation	Date of Event or Censoring	Outcome
1	Death before or on data cut off	Date of Death	Event
2	Death after data cut off	Date of data cut off	Censored
3	Subject still alive at data cut off	Date of data cut off	Censored
4	Subject lost to follow-up or withdraw of consent before data cut off	Date last known to be alive	Censored

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual lenvatinib plasma concentrations and nivolumab serum concentrations listings. The PK Analysis Set will be used for the summaries of lenvatinib plasma concentrations and nivolumab serum concentrations, for summaries and listings of PK parameters of lenvatinib.

5.5.1.1 Plasma or serum Concentration and its PK Parameter Analysis

<Concentration>

Plasma concentration values for lenvatinib and serum concentration values for nivolumab will be summarized by dose level using summary statistics (n, mean, standard deviation [SD], median, minimum [min] and maximum [max]) by nominal time point.

Plasma concentrations of lenvatinib, serum concentrations of nivolumab will be listed for each subject by actual sampling time.

<PK Parameter>

PK parameters will be derived by non-compartmental analysis using WinNonlin software (version 6.2.1 or later) according to 302-104.00-MNL.

The following pharmacokinetic parameters for lenvatinib will be calculated: C_{max} ,t_{max}, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}ti)}$, $AUC_{(0\text{-}inf)}$, $t_{½}$, CL/F, V_z/F, $C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, $AUC_{(0\text{-}\tau)}$, CL_{ss}/F, $C_{ss,av}$, $R_{ac}(C_{max})$, R_{ac}(AUC), PTF ratio and λ_z.

Other PK parameters may be calculated as appropriate.

Summary statistics will be tabulated for the PK parameters of lenvatinib by dose level. Summary statistics (n, mean, SD, median, min, and max) will be presented for all parameters (apart from t_{max} and $t_{ss,max}$ where mean and SD are not required). In addition, geometric mean and %CV will also be presented for all parameters apart from t_{max} and $t_{ss,max}$.

PK parameters of lenvatinib for each subject will be listed.

5.5.1.2 Pharmacokinetic Data Figures

The linear and semi-log plots of plasma concentration for lenvatinib and serum concentration for nivolumab versus actual time will be displayed by individual subjects. The actual time will be plotted on the X axis and the concentrations of lenvatinib and nivolumab will be plotted by dose level on the Y axis.

The linear and semi-log mean (+SD) plots of lenvatinib plasma concentration versus nominal time will be displayed. The nominal time will be plotted on the X axis and the mean (+SD)

will be plotted by dose level on the Y axis on the same graph by visit (Cycle 1 Day 1 and Cycle1 Day 15).

The linear and semi-log mean (+SD) plots of nivolumab serum concentration versus nominal time will be displayed. The nominal time will be plotted on the X axis and the mean (+SD) will be plotted on the Y axis on the same graph.

5.5.2 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. This analysis will be performed only when relavant biomarkers are evaluated and the analysis is deemed nesessary.

5.6 Safety Analyses

All DLT analyses will be performed on the DLT Analysis Set. 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).

5.6.1 Extent of Exposure

The parameters to be summarized are defined as follows.

These parameters for extent of exposure will be computed and presented for lenvatinib alone and nivolumab alone, separately.

For lenvatinib:

- Number of cycles = The last cycle with at least one lenvatinib dosing
- Duration of treatment (days) = Last dosing date – first dosing date + 1
- Duration of treatment (months) = (Last dosing date – first dosing date + 1) / (365.25/12)
- Number of subject-month with study drug dosing = Sum of duration of treatment (months) per subjects
- Total number of doses = Sum of days with lenvatinib dosing
- Total doses (mg) = Sum of all the actual dose
- Dose intensity (mg / days) = Total doses / Duration of treatment (days)
- Relative dose intensity (%) = 100 × Dose intensity / starting planned dose (8 or 12 mg)

For nivolumab:

- Number of cycles = The last cycle with at least one nivolumab dosing
- Duration of treatment (days) = Last dosing date with nivolumab – first dosing date + 1
- Duration of treatment (months) = (Last dosing date with nivolumab – first dosing date + 1) / (365.25/12)
- Number of subject-month with study drug dosing = Sum of duration of treatment (months) per subjects
- Total number of doses = Sum of days with nivolumab dosing
- Total doses (mg) = Sum of all the actual dose derived by [240 (mg) x (Actual volume infused (ml) / volume to be infused (ml))]
- Dose intensity (mg / 2weeks) = Total doses / ((Last dosing date with nivolumab – first dosing date + 14) / 14)
- Relative dose intensity (%) = 100 × Dose intensity / 240 (mg)

Number of cycles as combination therapy of lenvatinib and nivolumab will also be calculated and presented. The smaller number of cycles within a subject is defined as the number of cycle as combination therapy.

Furthermore, the following information of administration will also be summarized for both lenvatinib and nivolumab based on study medication data.

For lenvatinib, the number (percentage) of subjects who experienced a dose reduction and interruption will be summarized. For subjects who experienced a dose reduction, cycle of the first dose reduction will be summarized by descriptive statistics. Cycle of the first dose interruption will also be summarized in subjects who experienced a dose interruption. Frequency of dose reductions will be summarized by categories (1, 2, 3, ≥4). Frequency of dose interruptions will also be summarized by appropriate categories (e.g., 1, 2, 3, ≥4).

The date of dose reduction (from XX mg to YY mg, XX > YY > 0) is defined as the first date of planned dose of 0 mg followed by YY mg. The first date of 0 mg has to follow planned dose of XX mg. If the starting dose of YY mg does not follow 0 mg but XX mg, the first date of planned dose of YY mg is regarded as the date of dose reduction. Note that from 4 mg QD to 4mg QOD is also dose reduction.

The dose interruption is defined as the case where planned dose is 0 mg. The starting date of dose interruption is defined as the first date of planned dose of 0 mg following and followed by same dose level (> 0 mg). For example: 12 mg followed by 0 mg and followed by 12 mg; 8 mg followed by 0 mg followed by 8 mg. Successive days with planned dose of 0 mg is counted as one dose interruption event. If after dose 0 mg, the subject discontinued from lenvatinib permanently, it is not regarded as a drug interruption (but as a drug discontinuation).

An illustration for dose reduction and interruption in a subject is shown in Figure 2.

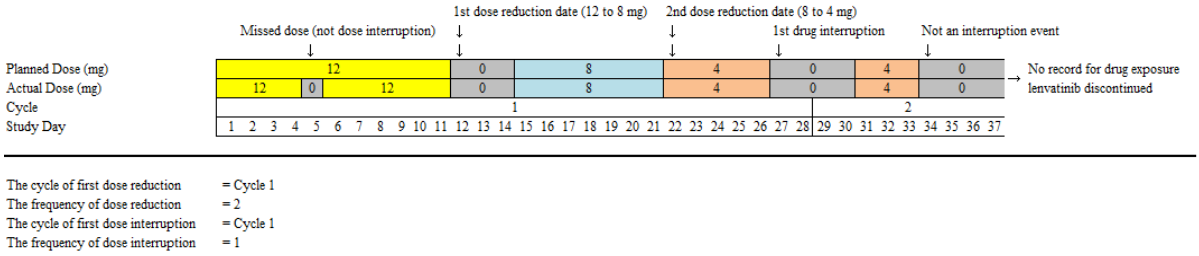


Figure 2 Dose reduction and interruption for lenvatinib

For nivolumab, the number (percentage) of subjects who experienced a dose interruption will be summarized. Cycle of first dose interruption will be summarized by descriptive statistics in subjects who experienced a dose interruption. Frequency of dose interruptions will be summarized by appropriate categories (e.g., 1, 2, 3, ≥4).

The dose interruption is defined as the case where planned dose of 0 mg. Successive dates with planned dose of 0 mg is counted as one dose interruption event, and the first date with

planned dose of 0 mg is defined as the starting date of dose interruption. If after dose 0 mg, the subject discontinued from nivolumab permanently, it is not regarded as a drug interruption (but as a drug discontinuation).

Subject data listings will be provided.

5.6.2 Dose Limiting Toxicity

The number and percentage of subjects with DLT will be calculated. DLT will also be summarized per type of toxicity.

Subject data listings will be provided.

5.6.3 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1 or later). 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) will also be captured in the database.

A treatment-emergent adverse event (TEAE), defined in the section 8.3, will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

An overview table, including the incidence of and the number of subjects with TEAEs, Treatment-related TEAEs, TEAEs with grade 3 or above, serious adverse events (SAEs), deaths, and TEAEs that led to discontinuation of lenvatinib, discontinuation of nivolumab, dose reduction of lenvatinib, dose interruption of lenbatinib and dose interruption of nivolumab will be provided.

The incidence of below events will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT.

- TEAEs
- TEAEs by the highest CTCAE grade
- TEAEs grade 3 or above
- Serious TEAEs
- Treatment-related TEAEs
- Treatment-related TEAEs by the highest CTCAE grade
- Treatment-related TEAEs grade 3 or above
- Treatment-related serious TEAEs
- TEAEs leading to discontinuation of lenvatinib

- TEAEs leading to dose reduction of lenvatinib
- TEAEs leading to dose interruption of lenvatinib
- TEAEs leading to discontinuation of nivolumab
- TEAEs leading to dose interruption of nivolumab

All deaths will also be summarized by primary reasons of deaths (progressive disease, AEs, others), deaths within 30 days of last dose of study drug, deaths >30 days of last dose of study drug, and treatment-related deaths.

Subject data listings of all deaths, SAEs, AEs leading to death, discontinuation of lenvatinib, discontinuation of nivolumab, dose reduction of lenvatinib, dose interruption of lenbatinib and dose interruption of nivolumab will be provided.

5.6.4 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using summary statistics. Qualitative parameters will be summarized by 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.

Box plot display will be used to show the longitudinal change of the parameters by visit.

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

Laboratory parameters will be graded by CTCAE ver. 4.03 in the section 13. Changes from CTCAE grade at baseline to each postbaseline visit and worst postbaseline will be reported using shift tables. CTCAE will also be used to identify subjects with Treatment-emergent markedly abnormal laboratory value (TEMAV). The number (percentage) of subjects with TEMAV (markedly abnormal high/low) will be summarized for each visit and overall study period. The changes from baseline to each postbaseline visit and overall study period will also be reported using shift tables. The TEMAV will be defined in the section 8.3.

Subject data listings will be provided.

5.6.5 Vital Signs

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

Box plot display will be used to show the longitudinal change of the parameters by visit.

Subject data listings will be provided.

5.6.6 Electrocardiograms

The results of ECG assessments performed at each visit will be evaluated. Summary statistics for ECG parameters (Heart Rate, RR, PR, QRS, QT, and QTcF) and changes from baseline will be presented by visit.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each visit.

In addition, the number (percentage) of subjects who met below criteria at least once in QTcF will be presented:

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

Subject data listings will be provided.

5.6.7 Other Safety Analyses

LVEF

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

Subject data listings will be provided.

ECOG PS

The number (percentage) of subjects for each category of ECOG PS will be summarized by visit. The highest postbaseline scale of ECOG PS for each subject will also be summarized.

Subject data listings will be provided.

5.7 Other Analyses

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 (ADA). If anti-nivolumab antibody develops, presence of neutralizing antibody will be summarized.

Subject data listings will be provided.

5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

6 INTERIM ANALYSES

No interim analysis will be conducted.

7 CHANGES IN THE PLANNED ANALYSES

A summary of all major additions, changes and deletions in the planned analyses described in the protocol will be provided in this section.

CCI [redacted]

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

8.1 General Data Handling

Definition of Baseline data

Baseline is defined as the last non-missing value observed prior to the first dose of study treatment for a given parameter.

Definition of Change from Baseline, Percent Change from Baseline

Change from baseline is defined as post-baseline value minus baseline value.
Percent change from baseline is defined as follows:

% Change from baseline = (Change from baseline / Baseline) * 100%

For any Baseline value of 0, the subject's corresponding percent change from baseline will not be included in the summary statistics table.

8.2 Efficacy Data Handling

Handling of missing data for tumor assessment result

For the analysis of ORR, DCR and CBR, subjects with missing response status (subjects whose baseline is missing and/or no adequate post-baseline tumor assessments result) will be coded as non-responders on Efficacy Analysis Set.

Rules for missing dates of tumor assessment or death

In case of dates missing in adverse event and concomitant medication collection following rules will be followed.

Data of tumor assessment result after documented PD or discontinuation from treatment

For the analysis of tumor assessment relevant efficacy endpoints, tumor assessment result after PD or final observation visit (for non-PD patients) are excluded from the analyses, but included in subject data listing.

8.3 Safety Data Handling

Treatment-emergent adverse event

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

- Reemerged during treatment, having been present at pretreatment but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

Adverse Events

Adverse Events with incomplete start dates will be considered treatment emergent if:

a. Day and month are missing and the year is equal to or after the year of the first dose date;

b. Day is missing, and the year is after the year of the first dose;

c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;

d. Year is missing;

e. Complete date is missing.

Concomitant Medications

Medications will be considered concomitant if:

a. Day and month are missing and the year is equal to or after the year of the first dose date;

b. Day is missing, and the year is after the year of the first dose;

c. Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date; or

d. Year is missing;

e. Complete date is missing.

TEMAV (Treatment-Emergent Markedly Abnormal Value)

Treatment-emergent markedly abnormal laboratory value (TEMAV) is defined as a postbaseline laboratory value with grade 3 or higher, and with a grade increase from baseline. (ie., Increasing grade 0 to 3 or higher, grade 1 to 3 or higher, grade 2 to 3 or higher, grade 3 to 4 or 5, grade 4 to 5.)

Handling of below lower quantification values in laboratory results

In the cases where laboratory result contains below lower quantification (BLQ) value, it will be replaced to the lower limit value of quantification (LLOQ) for summary tables.

The priority of use for blood pressure

For systolic and diastolic blood pressures, additional confirmatory assessment will be done more than 60 minutes after initial assessment, if necessary. In the case where there are both the initial and confirmatory assessment results in a day, confirmatory one will be used.

Calculation of creatinine clearance

To calculate a creatinine clearance (mL/min), the Cockcroft & Cault formula will be used.

Males: ((140 – age (years)) × weight (kg)) / (Creatinine (serum:mg/dL) × 72)

Females: ((140 – age (years)) × weight (kg) ×0.85) / (Creatinine (serum:mg/dL) × 72)

Visit Windows

The purpose of visit windows is to provide a single record per subject per visit for the calculation of descriptive statistics for safety parameters (e.g., laboratory values and vital signs, etc.) per scheduled visit, and change from baseline per visit. Other safety analyses (e.g., worst grade laboratory results) will include all observations.

The observation closest to the target date will be used in by visit summaries. If two or more observations have the same distance to the target visit day, the one that has the highest CTCAE grade or is furthest away from the normal range will be used for summary tables. If the multiple data in the same distance to the target date are in the same range from normal value, the data measured at an earlier date will be used for summary tables.

The visit window is applied for safety assessment item which is scheduled at each visit.

Analysis visit	Target Day	Visit Window	
		Start Day of Visit Window	End Day of Visit Window
Cycle 1 Day 8	Cycle 1 Day 1 + 7	Cycle 1 Day 1 + 5	Cycle 1 Day 1 + 9
Cycle 1 Day 15	Cycle 1 Day 1 + 14	Cycle 1 Day 1 + 12	Cycle 1 Day 1 + 16
Cycle 1 Day 22	Cycle 1 Day 1 + 21	Cycle 1 Day 1 + 19	Cycle 1 Day 1 + 23
Cycle 2 Day 1	Cycle 1 Day 1 + 28	Cycle 1 Day 1 + 28	Cycle 1 Day 1 + 31
Cycle 2 Day 8	Cycle 1 Day 1 + 35	Cycle 1 Day 1 + 32	Cycle 1 Day 1 + 38
Cycle 2 Day 15	Cycle 1 Day 1 + 42	Cycle 1 Day 1 + 39	Cycle 1 Day 1 + 45
Cycle 2 Day 22	Cycle 1 Day 1 + 49	Cycle 1 Day 1 + 46	Cycle 1 Day 1 + 52
Cycle n Day 1 (n ≥ 3)	Cycle n Day 1 + 28 x (n-1)	Cycle n Day 1 + 28 x (n-1) - 3	Cycle n Day 1 + 28 x (n-1) + 3

Cycle n Day 8 (n ≥ 3)	Cycle n Day 1 + 28 x (n-1) + 7	Cycle n Day 1 + 28 x (n-1) + 4	Cycle n Day 1 + 28 x (n-1) + 10
Cycle n Day 15 (n ≥ 3)	Cycle n Day 1 + 28 x (n-1) + 14	Cycle n Day 1 + 28 x (n-1) + 11	Cycle n Day 1 + 28 x (n-1) + 17
Cycle n Day 22 (n ≥ 3)	Cycle n Day 1 + 28 x (n-1) + 21	Cycle n Day 1 + 28 x (n-1) + 18	Cycle n Day 1 + 28 x (n-1) + 24
End of Treatment	30 days after last dose	Date of last dose	Date of last dose + 37

C1D1 is the day of first dosing.

8.4 Pharmacokinetic Data Handling

8.4.1 Lower Limit of Quantification of lenvatinib Plasma Concentration and Nivolumab Serum Concentration

The LLOQ of lenvatinib plasma concentrations is 0.250 ng/mL

The LLOQ of nivolumab serum concentrations is 0.200 μg/mL

8.4.2 BLQ Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, BLQ values will be handled according to 302-104.00-MNL, for non-compartmental pharmacokinetic analysis.

8.4.3 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.00-MNL for non-compartmental pharmacokinetic analysis.

8.4.4 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the SWP for non-compartmental pharmacokinetic analysis (302-104.00-MNL).

8.4.5 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD and coefficient variation (CV)) will have 3 significant digits. For t_{max} and $t_{ss,max}$, raw values and their median are shown in fixed 2 decimal places.

Variable	Unit	N	Digit rule	Raw/ Minimum/ Maximum	Mean Median	SD	Geometric Mean	CV (%)
drug concentration	ng/mL	X	Significant digits	3	3	3	-	-
C_{max}, $C_{ss,max}$, C_{min}, $C_{ss,av}$	ng/mL	X	Significant digits	3	3	3	3	3
t_{max}, $t_{ss,max}$	h	X	Fixed decimal places	2	2	-	-	-
λ_z(C1D1&D15)	1/h	X	Significant digits	3 (Listing only)	-	-	-	-
$t_{1/2}$(C1D1&D15)	h	X	Significant digits	3	3	3	3	3
$AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-ti)}$, $AUC_{(0-\tau)}$	ng•h/mL	X	Significant digits	3	3	3	3	3
CL/F, CL_{ss}/F	L/h	X	Significant digits	3	3	3	3	3
V_z/F(C1D1&D15)	L	X	Significant digits	3	3	3	3	3
R_{ac}		X	Significant digits	3	3	3	3	3
PTF ratio	%	X	Significant digits	3	3	3	3	3

Mean, SD, geometric mean and CV will not be calculated for t_{max}, $t_{ss,max}$.

CV(%)= sqrt(exp[SD**2 of log transformed data]-1)*100

NOTE

1. The following parameters are reported in the CSR, but appear in Listings only. They are important information to confirm that individual $t_{1/2}$ and its related parameters such as$AUC_{(0-inf)}$ are appropriately derived and allow those PK parameters to be reproduced when necessary.
   a. Time points used for estimation of λ_z (lower and upper)
   b. Number of the time points used for λ_z
   c. Adjusted regression coefficient (R_{2adj})

In Listings, a) are shown in same digits as actual sampling time after dosing used for calculation of PK parameters. For b), integer number is used in Listings. For c), significant 3 digits are used in Listing.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be conducted by Takumi Information Technology, using validated standard programs or double programming. For analyses needed in data review, single programming will be used.

All statistical analyses will be performed using SAS (version 9.3 or later). As necessary, other validated statistical software will also be used.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

- FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007 [internet; cited 3 March 2011] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

13 APPENDICES

13.1 National Institute for Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

National Cancer Institute (NCI) Cancer therapy evaluation program Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 May 2009 (v4.03 June 2010) is available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

CTCAE grades for selected laboratory parameters are listed in the table below, where ULN is the upper limit of normal and LLN is the lower limit of normal.

Lab Parameter	**NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units**				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hematology					
Hemoglobin (low)	100 - <LLN (g/L)	80 - <100 (g/L)	<80 (g/L)	__	Death
Hemoglobin (high)	Increase in >0 - 20 g/L above ULN (ie.., Increase in >0 - 2 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >20 - 40 g/L above ULN (ie.., Increase in >2 - 4 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >40 g/L above ULN (ie.., Increase in >4 gm/dL above ULN) or above baseline if baseline is above ULN	__	__
Platelet Count (PLT) (low)	75 - <LLN (x 10^9/L)	50 - <75 (x 10^9/L)	25 - <50 (x 10^9/L)	<25 (x 10^9/L)	__
White Blood Cell Count (WBC) (low)	3 - <LLN (x 10^9/L)	2 - <3 (x 10^9/L)	1 - <2 (x 10^9/L)	<1 (x 10^9/L)	__
White Blood Cell Count (WBC) (high)	__	__	>100 x 10^9/L (ie.., >100,000/mm^3)	__	Death
Lymphocytes (low)	0.8 - <LLN (x 10^9/L)	0.5 - <0.8 (x 10^9/L)	0.2 - <0.5 (x 10^9/L)	<0.2 (x 10^9/L)	__
Lymphocytes (high)	__	>4 - 20 (x 10^9/L) (ie.., >4,000 - 20,000/mm^3)	>20 (x 10^9/L) (ie.., > 20,000/mm^3)	__	__
Neutrophils (low)	1.5 - <LLN (x 10^9/L)	1 - <1.5 (x 10^9/L)	0.5 - <1 (x 10^9/L)	<0.5 (x 10^9/L)	__

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blood Coagulation					
INR (high)	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	__	__
Blood Chemistry					
Albumin (low)	30 - <LLN (g/L)	20 - <30 (g/L)	<20 (g/L)	__	Death
Alkaline Phosphatase (ALP) (high)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
ALT (SGPT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
AST (SGOT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
Total Bilirubin (high)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	__
Calcium, serum-low (hypocalcemia)	2.0 - <LLN (mmol/L) (ie.., 8.0 mg/dL - <LLN) *	1.75 - <2 (mmol/L) (ie.., 7.0 - <8.0 mg/dL) *	1.5 - <1.75 (mmol/L) (ie.., 6.0 - <7.0 mg/dL) *	<1.5 (mmol/L) (ie.., <6.0 mg/dL) *	Death
Calcium, serum-high (hypercalcemia)	>ULN – 2.9 (mmol/L) (ie.., >ULN – 11.5 mg/dL) *	>2.9 – 3.1 (mmol/L) (ie.., >11.5 – 12.5 mg/dL) *	>3.1 – 3.4 (mmol/L) (ie.., >12.5 – 13.5 mg/dL) *	>3.4 (mmol/L) (ie.., >13.5 mg/dL) *	Death
Cholesterol (high)	>ULN -7.75 mmol/L	>7.75 -10.34 mmol/L	>10.34 -12.92 mmol/L	>12.92 mmol/L	__
CPK (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	__
Creatinine (high)	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN	>6.0 x ULN	__
GGT (gamma-glutamyltransferase) (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5.0 x ULN	>5.0 x ULN – 20.0 x ULN	>20.0 x ULN	__
Glucose, serum-low (hypoglycemia)	3 - <LLN (mmol/L)	2.2 - <3 (mmol/L)	1.7 - <2.2 (mmol/L)	<1.7 (mmol/L)	Death

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Glucose, serum-high (hyperglycemia)	ULN – 8.9 (mmol/L)	>8.9 – 13.9 (mmol/L)	>13.9 – 27.8 (mmol/L)	>27.8 (mmol/L)	Death
Lipase (high)	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	__
Magnesium (low)	<LLN – 0.5 (mmol/L)	<0.5 – 0.4 (mmol/L)	<0.4 – 0.3 (mmol/L)	<0.3 (mmol/L)	Death
Magnesium (high)	>ULN – 1.23 (mmol/L)	__	>1.23 – 3.30 (mmol/L)	>3.30 (mmol/L)	Death
Triglyceride (hypertriglyceridemia) (high)	1.71 – 3.42 (mmol/L)	>3.42 – 5.7 (mmol/L)	>5.7 – 11.4 (mmol/L)	>11.4 (mmol/L)	Death
Phosphate, serum-low (hypophosphatemia)	0.8 - <LLN (mmol/L)	0.6 - <0.8 (mmol/L)	0.3 - <0.6 (mmol/L)	<0.3 (mmol/L)	Death
Potassium, serum-low (hypokalemia)	3.0 - <LLN (mmol/L)	__	2.5 - <3.0 (mmol/L)	<2.5 (mmol/L)	Death
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 (mmol/L)	>5.5 – 6.0 (mmol/L)	>6.0 – 7.0 (mmol/L)	>7.0 (mmol/L)	Death
Uric Acid (hyperuricemia) (high)	>ULN – 590 (umol/L)	__	__	>590 (umol/L)	__
Sodium, serum-low (hyponatremia)	130 - <LLN (mmol/L)	__	120 - <130 (mmol/L)	<120 (mmol/L)	Death
Sodium, serum-high (hypernatremia)	>ULN - 150 (mmol/L)	>150 - 155 (mmol/L)	>155 - 160 (mmol/L)	>160 (mmol/L)	Death
Urinalysis					

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Proteinuria (high)	1+ proteinuria; urinary protein <1.0 g/24 hrs	≥2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs	urinary protein >=3.5 g/24 hrs	—	—

* Corrected serum calcium by albumin should be referred. If serum albumin is <4.0 g/dL, the corrected calcium will be calculated using the following formula: Corrected calcium (mg/dL) = Total calcium (mg/dL) – 0.8 x [Albumin (g/dL) – 4]

SIGNATURE PAGE

Author:

PPD
PPD
Medicine Development Center

Date

Approval:

PPD PPD
PPD
PPD
Medical Development Center

Date

Study Director

PPD
PPD
Oncology Business Group

Date

Pharmacokinetic Analyst

PPD
PPD
Medicine Development Center

Date

SIGNATURE PAGE

Author:

PPD

17 Jan 2018
Date

Medicine Development Center

Approval:

PPD

17 Jan2018
Date

Medical Development Center

PPD

17. Jan. 2018
Date

Study Director

PPD

PPD Oncology Business Group

PPD

17 Jan2018
Date

tic Analyst

PPD

PPD Medicine Development Center