STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7080-J081-115
Study Protocol Title:	An Open-Label Phase 1b Trial of Lenvatinib Plus Pembrolizumab in Subjects with Selected Solid Tumors
Date:	11 Oct 2019
Version:	Version 3.0

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ATC	anatomical therapeutic chemical
BOR	best overall response
BTC	biliary tract cancer
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
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
LLT	lower level term
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NE	not evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	pharmacodynamics
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
QT	QT interval
RECIST	response evaluation criteria in solid tumor
SAP	statistical analysis plan
SD	stable disease
SI	système international
SOC	system organ class

Abbreviation	Term
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TLG	tables, listings, and graphs
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-J081-115 (Amendment 02).

3.1 Study Objectives

3.1.1 Primary Objective

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

3.1.2 Secondary Objectives

To evaluate the following efficacy endpoints by Immune-related Response Evaluation Criteria In Solid Tumors (irRECIST) and modified RECIST 1.1:

- Objective response rate (ORR)
- Duration of response (DOR)

To assess the pharmacokinetic (PK) profile of lenvatinib and pembrolizumab

To detect anti-drug antibodies for pembrolizumab (ADA)

3.1.3 Exploratory Objective

- To evaluate the following efficacy endpoints by irRECIST and modified RECIST 1.1:

  - Progression-free survival (PFS)

  - Time to response (TTR)

  - Disease control rate (DCR)

  - Clinical benefit rate (CBR)

- To investigate the relationship between candidate biomarkers and anti-tumor activity of lenvatinib in combination with pembrolizumab:

- To explore blood and tumor markers (such as programmed cell death protein 1 ligand 1 [PD L1] expression levels, cytokine and angiogenic factor profiling), and immune cell profiling and evaluate their relationship with clinical outcomes including anti-tumor activity of lenvatinib in combination with pembrolizumab.

3.2 Overall Study Design and Plan

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

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

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

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

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

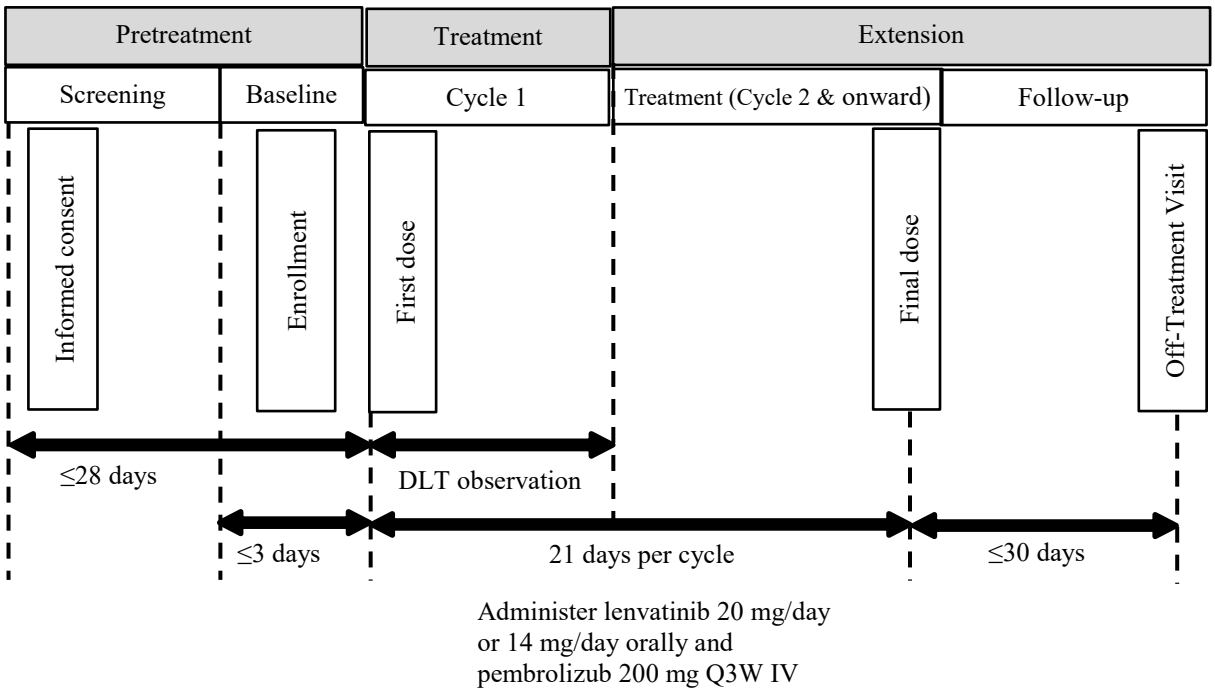
If there is a potential subject who is not evaluable for DLT (eg, subject who fails to administer ≥75% of the planned dosage of lenvatinib due to a reason other than treatment related toxicity during Cycle 1), the investigator and sponsor will discuss whether or not to include the subject in the DLT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

The study will be conducted in 3 phases: a Pretreatment Phase, a Treatment Phase, and an Extension Phase (Figure 1).

- The **Pretreatment Phase** will last no longer than 28 days and will include a Screening Period and a Baseline Period.

- The **Treatment Phase** consists of the first cycle (21 days) for each subject. The Treatment Phase for each subject ends after they complete Cycle 1 of treatment or if they discontinue early. Those subjects who discontinue study treatment in Cycle 1 transition to the Off Treatment (Off-Tx) Visit of the Follow-up Period of the Extension Phase. Those who complete Cycle 1 transition to the Treatment Period of the Extension Phase.

- The **Extension Phase** begins after a subject completes Cycle 1 and ends when the subject completes the Off-Tx Visit. Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor termination of the study. The Extension Phase consists of 2 periods, the Treatment Period and the Follow-up Period.



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

Figure 1 Study Design

4 DETERMINATION OF SAMPLE SIZE

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

5 STATISTICAL METHODS

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.

5.1 Study Endpoints

The efficacy endpoints based on irRECIST and ORR (Week 24) were defined in protocol but excluded from the analyses. According to ongoing clinical data, analyses based on irRECIST were almost same as ones based on mRECIST. ORR (Week 24) is to be same as ORR.

5.1.1 Primary Endpoint

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

5.1.2 Secondary Endpoints

The secondary endpoints related to the efficacy endpoints will be ORR and DOR by modified RECIST 1.1. These efficacy endpoints are defined as follows.

- ORR is defined as the proportion of subjects who have BOR of CR or PR at the time of data cutoff.
- DOR is defined as the time from the first documentation of CR or PR to the date of first documentation of disease progression (based on modified RECIST 1.1) or death (whichever occurs first).

Determination of the PK profile of lenvatinib and pembrolizumab while subjects are receiving combination therapy.

Serum ADA will be also measured.

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

$AUC_{(0\text{-}inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$t_{1/2}$	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
$AUC_{(0\text{-}\tau)}$	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

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

- PFS is defined as the time from the first study dose date to the date of first documentation of disease progression (based on modified RECIST 1.1) or death (whichever occurs first). If a subject has not experienced disease progression or death, then the subject's data will be censored at the date of the last available tumor assessment.
- TTR is defined as the time from the date of first study dose to the date of first documentation of CR or PR.
- DCR is defined as the proportion of subjects who have BOR of CR or PR or SD (minimum duration from C1D1 to SD ≥5 weeks).
- CBR is defined as the proportion of subjects who have BOR of CR or PR or durable SD (duration of SD ≥23 weeks).

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

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

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

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

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

The number of subjects enrolled, the number (percentage) of subjects included in each analysis set will be presented for overall subjects. 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 (i.e., 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 treatment, and the reason for the study treatment discontinuation. Subject disposition table will be presented for overall subjects.

A subject who completed the study treatment in extension phase is defined as a subject who is still continuing study treatment at the time of study cut-off or discontinued treatment due to disease progression.

Subject data listings will be provided.

5.2.3 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major and minor 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 be included in TLGs covered by SAP and presented in the clinical study report (CSR).

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for overall subjects using descriptive statistics. This summary table will be generated on the Safety Analysis Set, DLT Analysis Set and the PK Analysis Set.

Continuous demographic and baseline variables include

- age
- height
- weight

Categorical demographic and baseline variables include

- age group (<65 years, ≥65 to <75 years, ≥75 years)
- sex
- race
- ethnicity
- country
- ECOG-PS
- NYHA (I, II, III, IV and NA for Heart failure)

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

- Primary tumor
- Diagnostic information
  - TNM staging
- Time since original diagnosis to the first dose
- Time since last disease progression to the first dose
- Known mutation status (EGFR, KRAS, NRAS, BRAF)

Prior anticancer therapies will be summarized by:

- Number of prior regimen
- Type of previous therapy (adjuvant, neoadjuvant, metastatic, locally advanced, maintenance, unknown)
- Best response for last anti-cancer therapy (CR, PR, SD, PD, NE, NA, unknown)
- Duration of last therapy (months)
- Time from end of last therapy to study entry (months)

Prior radiotherapy will be summarized by:

- Subjects with any prior radiotherapy
- Tumor lesion at the site progressed since radiotherapy (yes, no, not evaluated)
- Time from last radiotherapy to date of treatment (months).

Prior anticancer procedure will be presented in subject data listing.

Subject data listings for demographic and other baseline characteristics 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 drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose or until the subject initiates new anticancer therapy, whichever is earlier. The other medications are defined as post-treatment medications.

The following summary table will be presented for overall subjects on the Safety Analysis Set.

The number (percentage) of subjects who took prior anti-cancer medications (ie., anti-cancer medications and anti-cancer procedures) will be summarized by Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term for overall subjects.

The number (percentage) of subjects who took prior and concomitant medications (ie., all medication and non-pharmacological procedure) will be summarized by Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term for overall subjects.

All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Treatment related protocol deviations will be presented in CSR as provided in section "5.2.3 Protocol Deviations " but will not be included in TLGs covered by SAP.

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 section 8.

5.3.6 Other Considerations

Not applicable.

5.4 Efficacy Analyses

All efficacy analyses will be summarized with available data in the clinical database at the data cutoff. The efficacy analysis will be performed based on the Efficacy Analysis Set. Efficacy data will be presented for overall subjects.

5.4.1 Efficacy Analyses

All efficacy endpoints will be based on the tumor assessments performed by the investigators using modified RECIST 1.1. Based on the tumor assessment criteria, BOR will be summarized, and ORR and its corresponding exact 2-sided 95% confidence interval (CI) will be calculated. Responses of PR or CR have to be confirmed no less than 4 weeks after the initial response in this study. DOR will also be summarized and plotted over time by Kaplan-Meier method. The analysis for DOR will be performed in the subjects whose response of PR or CR is confirmed.

Likewise, PFS and TTR will be analyzed as needed. If applicable, DCR, CBR, and their corresponding exact 2-sided 95% CI will also be calculated. A waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at postbaseline nadir (ie, maximum tumor shrinkage).

The percent changes from baseline over time in the sum of the diameters of target lesions will be presented using by spider plot.The definition of DOR, PFS, TTR and durable SD will be as follows:

- DOR (days) = Date of first documented PD/ death/ censored date (whichever occurs first) – Date of first evaluation of PR or CR + 1.
- PFS (days) = Date of first documented PD/ death/ censored date (whichever occurs first) – Date of first dose + 1.
- TTR (days) = Date of first documented CR or PR (whichever occurs first) – Date of first dose + 1.
- Durable SD = duration of SD ≥23 weeks

- ✧ Duration of SD is defined as the time from the date of first dose to the first documented PD or death, whichever occurs first.

The censoring rules for DOR and PFS are detailed in section 8.

Subject data listings will be provided.

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, pembrolizumab serum concentrations and ADA levels listings. The PK Analysis Set will be used for the summaries of lenvatinib plasma concentrations and pembrolizumab serum concentrations and for summaries and listings of PK parameters of lenvatinib. The data in patient with dose-reduction/interruption will not be included on calculation of summary statistics. Analysis of pembrolizmab serum concentrations and ADA levels will be performed and detailed in a separate report by Merck & Co., Inc.

5.5.1.1 Plasma or serum Concentration and its PK Parameter Analysis

<Concentration>

Plasma concentration values for lenvatinib and serum concentration values for pembrolizumab will be summarized 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 pembrolizumab and ADA levels will be listed for each subject by actual sampling time.

<PK Parameter (Lenvatinib Only)>

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}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $t_{1/2}$, λ_z, CL/F, V_z/F, MRT, $C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, $AUC_{(0-\tau)}$, CL_{ss}/F, $C_{ss,av}$, $R_{ac}(C_{max})$, R_{ac}(AUC), PTF.

Other PK parameters may be calculated as appropriate.

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

Summary statistics will be tabulated for the PK parameters of lenvatinib. 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 the linear plots of serum concentration for pembrolizumab 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 pembrolizumab will be plotted 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 on the Y axis on the same graph by visit (Cycle 1 Day 1 and Cycle1 Day 15).

The linear mean (+SD) plots of pembrolizumab 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.

5.6 Safety Analyses

All tolerability analyses will be performed on the DLT Analysis Set. Safety analyses will be performed on the Safety Analysis Set. Tolerability and safety data will be presented for overall subjects as appropriate by using summary statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; number [percentage] for categorical variables).

5.6.1 Extent of Exposure

The parameters to be summarized are defined as follows. The parameters for extent of exposure will be computed for combination (lenvatinib plus pembrolizumab), lenvatinib alone and pembrolizumab alone, respectively.

1. Number of cycles of Lenvatinib = Round down "(last dosing date – first dosing date) / 21 + 1" to integer.
2. Number of cycles of Pembrolizumab = Round "(last dosing date – first dosing date + 1) / 21 + 1" to integer.
3. Number of cycles of combination treatment = Larger number of cycle of each study drug.
4. Duration of treatment (days) = Last dosing date – first dosing date + 1
5. Duration of treatment (months) = (Last dosing date – first dosing date + 1) / (365.25/12)
6. Total doses (mg) of Lenvatinib = Sum of all the actual dose

7. Total doses (mg) of Pembrolizumab = Sum of all the actual dose derived by [Planned dose (mg) x (Actual volume infused (ml) / volume to be infused (ml))]
8. Dose intensity of Lenvatinib (mg / (days)) = Total doses / Duration of treatment
9. Dose intensity of Pembrolizumab (mg / (Q3W)) = Total doses / No. of cycles
10. Relative dose intensity (%) = 100 × Dose intensity / starting planned dose

The following tables will provide the parameters to be calculated for the study drug.

Lenbatinib plus Pembrolizumab	Lenvatinib	Pembrolizumab
3, 4*, 5* *: defined as the duration between the earliest first dose start date of either medication and the latest last dose end date of either medication	1, 4, 5, 6, 8, 10	2, 4, 5, 7, 9, 10

Furthermore, the following information of administration will also be summarized for each drug, lenvatinib and pembrolizumab.

The number (percentage) of subjects who experienced dose reductions and treatment interruptions will be summarized based on actual dose record from study medication data. The analysis for dose reduction will be performed only for lenvatinib.

Time to first dose reduction of lenvatinib (weeks) and interruption of pembrolizumab (cycles) will be summarized by descriptive statistics for subjects with dose reduction/interruption event. Summary for all subjects will also be provided using Kaplan-Meier method. For subjects without dose reduction/interruption event, the time to dose reduction/interruption is censored at the last dosing date.

Frequency of dose interruptions will also be summarized by appropriate categories (e.g., 1, 2, 3, ≥4).

Frequency of dose reductions will be summarized by categories (1, 2, 3, 4).

- Definition of Dose Reduction of Lenvatinib:
  - Dose level reduces from previous dose level after dose interruption period per Protocol. For example, 24 mg followed by 0 mg followed by 20 mg; 20 mg followed by 0 mg followed by 14 mg.

- If the reduced dose level starts without dose interruption period, that case is also counted as dose reduction event.

- Definition of Dose interruption of Lenvatinib:

  - Only include the scenario that the before and after dose 0 (interruption period), the dose levels are the same. For example: 24 mg followed by 0 mg and followed by 24 mg; 20 mg followed by 0 mg followed by 20 mg.

  - If dose level reduces from previous dose level after dose interruption period (dose 0), it should be counted into dose reduction, but not dose interruption. For example, 24 mg followed by 0 mg followed by 20 mg, the period with 0 mg should not be counted into dose interruption, but instead should be counted as a dose reduction.

  - If after dose 0 mg, the subject discontinued from treatment permanently, it should be counted as a treatment discontinuation instead of a dose interruption.

- Definition of Dose Interruption of Pembrolizumab:

  - The record of 0 mg dosed is counted as the dose interruption event.

The actual dosing transition and duration of both study drug with tumor response is presented using swimmer plot.

Subject data listings will be provided.

5.6.2 Dose Limiting Toxicity

The number (percentage) of subjects who experienced DLT will be summarized. The category of DLT will also be summarized.

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 19.0 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 “8.1 General Data Handling”, will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

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 treatment discontinuation, dose reduction, or dose interruption 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 CTCAE grade
- TEAEs grade 3 or above
- Serious TEAEs
- Treatment-related TEAEs
- Treatment-related TEAEs by 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 Pembrolizumab
- TEAEs leading to dose interruption of Pembrolizumab
- TEAEs leading to discontinuation of Lenvatinib or Pembrolizumab
- TEAEs leading to dose interruption of Lenvatinib or Pembrolizumab

The the number (percentage) of subjects with TEAEs will also be reported by MedDRA PT in descending order.

Subject data listings of all deaths, SAEs, AEs leading to death, treatment discontinuation, dose reduction, or dose interruption will be provided. All AE regardless of treatment-emergent or not will be included in the subject data listings.

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 and whisker plot 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. Changes from CTCAE grade at baseline to each postbaseline visit and worst postbaseline will be reported using shift tables.

CTCAE ver. 4.03 will 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, respiratory rate, and temperature), and weight and changes from baseline will be presented by visit.

Box and whisker plot 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

LVEF and change from baseline 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

Not applicable.

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 or previous version of SAP will be provided in this section.

The efficacy endpoints based on irRECIST and ORR (Week 24) were defined in protocol but excluded from the analyses. According to ongoing clinical data, analyses based on irRECIST were almost same as ones based on mRECIST. ORR (Week 24) is to be same as ORR.

The definition of concomitant medications are aligned with protocol's assessment rule.

Pharmacokinetic analysis:

- Manual number of non-compartmental analysis was revised from 302-104.00 to 302-104.01

  Section 5.5.1

- "The data in patient with dose-reduction/interruption will not be included on calculation of summary statistics." was added.
- "Analysis of pembrolizmab serum concentrations and ADA levels will be performed and detailed in a separate report by Merck & Co., Inc." was added.
- PK parameter; Calculation of $AUC_{(0\text{-}ti)}$ was deleted. Calculation of λ_z and MRT was added.

  Section 8.4

- The LLOQ of lenvatinib plasma concentration was revised from 0.250 to 0.100 ng/mL.
- General Rules for Presentation of Drug Concentrations and PK Parameters was updated.

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 on or 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.

Handling of data not within specified periods or within the follow-up period

All the safety parameters will be used for summary statistic tabulation, except when it is irrelevant like the situation that tests scheduled to be conducted before administration of the investigational drug were actually conducted after its administration.

8.2 Efficacy Data Handling

Handling of missing data

For the analysis of response rates (proportion of subjects whose best overall response on tumor assessment is PR, CR, SD or dSD), subjects with missing response status (subjects whose baseline or post-baseline tumor assessment is missing) will be coded as non-responders on Efficacy Analysis Set.

Censoring rules for PFS

The following table provides the censoring rules for PFS.

No.	Situation	Date of Event (Progression/Death) or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored

2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
3	No progression at the time of data cut-off	Date of last adequate radiologic assessment before or on date of data cut-off	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Event
6	Death between adequate assessment visits*	Date of death	Event
7	Death or progression after more than one missed visit/tumor assessment**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

CR = complete response, PD = progressive disease, PR = partial response, SD =stable disease,

* Adequate tumor assessment is radiologic assessment of CR, PR, SD, non-CR/non-PD, or PD at regular interval as defined in the protocol.

** More than one missed visit/adequate tumor assessment is defined as having either one of the following two durations being longer than 12 weeks + 2weeks (ie, the date of death or PD – the date of last adequate tumor assessment > 97 days) for subjects on the every 6 week tumor assessment schedule in the first 8 cycles of treatment and 18 weeks + 2 weeks (ie, the date of death or PD – the date of last adequate tumor assessment > 139 days) for subjects on the every 9 week tumor assessment schedule after Cycle 8 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 a baseline tumor assessment (No. 1), the subject will be censored on the date of first dose. However, if the subject died within 97 days (14 weeks -1 day) after first dose and did not receive a new anticancer treatment, it will be counted as PFS event at the date of death. If a subject had new anticancer treatment before PD or death (No. 4), 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 tumor assessments before PD or death (No. 7), 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 criterion (No.4), the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), 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, No. 3, No. 4, or No. 7).

Censoring rules for DOR

The censoring rules for DOR will be employed same rule as PFS.

8.3 Safety Data Handling

Definition of derived variables for extent of exposure

The derivation rule will be presented in the section 5.6.1.

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.

TEMAV (Treatment-Emergent Markedly Abnormal Value)

The treatment-emergent markedly abnormal laboratory values (TEMAV) will be summarized using CTCAE grade 3 and 4 postbaseline test results.

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.

Visit Windows for Safety Analyses

The analysis window for safety analysis is based on the visits recorded in CRF. In the calculation of descriptive statistics for safety parameters (eg, laboratory values and vital signs, etc.) per scheduled visit, and change from baseline per visit, if multiple observations fall in the same scheduled visit, the first record will be used for summary tables. Other safety analyses (eg, worst grade laboratory results) will include all observations until the date of 30 days following the last dose of study drug.

8.4 Pharmacokinetic Data Handling

8.4.1 Lower Limit of Quantification of lenvatinib Plasma Concentration and Everolimus Blood and Concentration

The LLOQ of lenvatinib plasma concentrations is 0.100 ng/mL

The LLOQ of pembrolizumab serum concentrations is 25 ng/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}, $C_{ss,max}$, $C_{ss,min}$, $C_{ss,av}$	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	3	3	3	3
$t_{1/2}$(C1D1&D15)	h	X	Significant digits	3	3	3	3	3
$AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-\tau)}$	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
MRT	h	X	Significant digits	3	3	3	3	3

R_{ac}		X	Significant digits	3	3	3	3	3
PTF	%	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 $AUC_{(0\text{-inf})}$ 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 $AUC_{(0\text{-inf})}$ obtained by extrapolation ($\%AUC_{ex}$)
   e. The last time points used for calculation of $AUC_{(0\text{-t})}$ (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.

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

All statistical analyses except pembrolizumab PK and ADA related ones 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) and WinNonlin (version 6.2.4 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: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

SIGNATURE PAGE

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