STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7080-A001-111 (Phase 1b/2)
Study Protocol Title:	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors
Date:	September 16, 2020
Version:	Final 4.0

SUMMARY OF CHANGES FROM SAP VERSIONS 3 TO 4

Version 4 Date: 16 Sep 2020

Change	Rationale
The pharmacokinetic (PK)/pharmacodynamics (PD) analyses are removed; and changes in PK analyses was made.	To reflect analysis-related changes that were made in the protocol amendment 08.

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BLQ	Below limit of quantification
BMI	Body mass index
BOR	Best overall response
C#/D#	Cycle#/Day#
CBR	Clinical benefit rate
CI	Confidence interval
CR	Complete response
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	Diastolic blood pressure
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
DTC	Differentiated thyroid cancer
ECG	Electrocardiogram
FDA	Food and Drug Administration (Washington, DC, USA)
INR	International normalized ratio
irRECIST	Immune-related RECIST
ITT	Intention-to-treat

Abbreviation	Term
IV	Intravenous
MTD	Maximum tolerated dose
KM	Kaplan-Meier
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MUGA	Multiple Gated Acquisition
NA	Not applicable
NE	Not evaluable
NYHA	New York Heart Association
Off-Tx	Off Treatment
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD	Pharmacodynamic
PD-L1	Programmed Death-Ligand 1
PFS	Progression-free survival
PID	Percent intended dose
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
Q3W	Every 3 weeks

Abbreviation	Term
QD	Once a day
QT	Time from the beginning of the QRS complex to the end of the T wave
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SD	Stable disease
SI	Système international
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLG	Tables, listings, and graphs
TNM	Tumor-node-metastasis
ULN	Upper limit of normal

3 INTRODUCTION

The Eisai Protocol E7080-A001-111 is a multicenter, open-label Phase 1b/2 trial of lenvatinib (E7080) plus pembrolizumab in subjects with selected solid tumors. This statistical analysis plan (SAP) describes the procedures and the statistical methods that will be used to analyze and report results for the Phase 1b/2 of Eisai Protocol E7080-A001-111 except those for pharmacokinetic (PK), pharmacodynamics (PD) and biomarkers. This SAP is based on the clinical study protocol amendment 8 (dated 24 Aug 2020).

3.1 Study Objectives

3.1.1 Primary Objectives

The primary objectives are

- Phase 1b – Determination and confirmation of the maximum tolerated dose (MTD):
  To determine and confirm the MTD for lenvatinib in combination with 200 mg (intravenous [IV], every 3 weeks [Q3W]) pembrolizumab in subjects with selected solid tumors.
- Phase 2 – Expansion in selected tumor types (Expansion):
  To evaluate the objective response rate as of Week 24 ($ORR_{(Week\ 24)}$: complete response + partial response [$CR_{(Week\ 24)}$ + $PR_{(Week\ 24)}$]) of lenvatinib in combination with pembrolizumab in each of the cohorts, using immune-related RECIST (irRECIST).

3.1.2 Secondary Objectives

The secondary objectives for both Phase 1b and 2 are to assess:

- The tolerability and safety profile of lenvatinib in combination with pembrolizumab
- ORR by irRECIST of lenvatinib in combination with pembrolizumab in subjects with solid tumors
- Progression-free survival (PFS) by irRECIST
- Overall survival (OS)
- Duration of response (DOR) by irRECIST
- Disease control rate (DCR: CR + PR + stable disease [SD]) by irRECIST
- Durable stable disease rate (durable SD [SD ≥23 weeks]) by irRECIST

- Clinical benefit rate (CBR: CR, PR + durable SD) by irRECIST
- The Pharmacokinetic (PK) profile of lenvatinib during combination treatment.

3.1.3 Exploratory Objectives

Exploratory objectives are:

- To explore tumor response (eg, PR, CR, SD, PD) based on modified RECIST 1.1 assessments
- To explore tumor response in subjects with endometrial carcinoma and renal cell carcinoma based on independent imaging review (IIR) using irRECIST, modified RECIST 1.1 and RECIST 1.1.
- To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of lenvatinib in combination with pembrolizumab:
    a. To evaluate the relationship between PD-L1 (Programmed Death-Ligand 1) expression levels and other relevant biomarkers (eg, tumor infiltrating lymphocytes, T-cell repertoire, ribonucleic acid [RNA] signature profiles) in tumor samples and anti-tumor activity of lenvatinib in combination with pembrolizumab.
    b. To evaluate differences in tumor tissue characteristics in biopsies taken post treatment with lenvatinib in combination with pembrolizumab versus baseline

3.2 Overall Study Design and Plan

This is a multicenter, open-label Phase 1b/2 trial of lenvatinib (E7080) plus pembrolizumab in subjects with selected solid tumors.

Phase 1b - MTD: This phase will determine and confirm the MTD of lenvatinib in combination with pembrolizumab. Ten to 30 subjects will be enrolled in Phase 1b. Subjects in Phase 1b will have the following tumors: non-small cell lung cancer, renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma. The dose of pembrolizumab 200 mg every 3 weeks IV will not change during the MTD phase, while the second study drug lenvatinib will start at 24 mg and then be reduced, if necessary, to either 20 mg or 14 mg.

For determination of MTD, only dose limiting toxicities (DLTs) during the first cycle of

treatment will be assessed. If 0 of 3 subjects in a given dose level cohort experiences a DLT, then 7 more subjects will be enrolled into that dose level to confirm the MTD. If 1 of 3 subjects has a DLT, then 3 more subjects will be enrolled into that dose level for a total of 6 subjects. If only 1 of these 6 subjects has a DLT, then 4 more subjects will be enrolled into that dose level to confirm the MTD. If 2 or more of these 6 subjects at a dose level experience a DLT, then, following consultation with the principal investigator(s) the study will proceed with enrollment in the next defined lower dose, with dose reduction of lenvatinib to 20 or 14 mg once a day (QD), respectively, in combination with 200 mg pembrolizumab Q3W.

The MTD will be confirmed if no more than 3 of 10 subjects experience DLTs at a dose level during the first 3 weeks (Cycle 1) of treatment. If the MTD is not confirmed at a dose level, then enrollment will proceed to the next lower dose level. The sponsor and investigators will review all subjects' safety and clinical data to jointly determine the recommended Phase 2 dose (RP2D) of the combination of lenvatinib with pembrolizumab. If 2 or more subjects have a DLT in Dose Level 3, enrollment in the study will stop.

Phase 2 - Expansion: After the MTD is confirmed, and depending on the safety and efficacy observed, 6 cohorts will be enrolled. Each of these cohorts will enroll subjects with only 1 type of tumor (ie, non-small cell lung cancer, predominantly clear cell renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, melanoma (excluding uveal melanoma), or squamous cell carcinoma of the head and neck). Lenvatinib in combination with pembrolizumab will be administered at the RP2D. The intent is to enroll 20 subjects in each of the 6 cohorts, with possible expansion of enrollment in the endometrial and renal cell carcinoma cohorts. For all 6 cohorts, data from the first 10 subjects in each cohort will be reviewed by the sponsor and investigators. At least 3 subjects must show responses in order to determine continued enrollment to 20 evaluable subjects.

The endometrial carcinoma and renal cell carcinoma cohorts will be further expanded to approximately 120 evaluable subjects. The decision to expand enrollment will be based on the efficacy results of 2 interim analyses. The details of the cohort expansions are provided in Section 3.

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

Pretreatment Phase: This phase will last no longer than 28 days and includes: a Screening Period, to obtain informed consent and establish protocol eligibility, and a Baseline Period, to confirm protocol eligibility prior to treatment.

Treatment Phase: This phase will begin with the administration of the first dose of study drug in Cycle 1 and will continue in 21-day (3-week) cycles. The Treatment Phase consists of 1 treatment period as described below.

Treatment Period in Phase 1b: The Treatment Period for each subject ends after completing Cycle 1 of treatment or 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.

Treatment Period in Phase 2: The Treatment Period for each subject ends after completing 8 cycles of treatment unless the subject discontinues early. Those who discontinue study treatment before completing 8 cycles transition to the Off-Tx Visit of the Follow-up Period of the Extension Phase. Those that complete 8 cycles transition to the Treatment Period of the Extension Phase.

Extension Phase: The Extension Phase consists of a treatment period and a follow-up period.

Treatment Period (Extension Phase): Subjects still receiving study treatment at the end of the Treatment Phase will continue to receive the same treatment. Those subjects that discontinue study treatment transition to the Off-Tx Visit of the Follow-up Period of the Extension Phase. Note that all AEs must be captured for 30 days after last dose of study treatment.

Follow-up Period (Extension Phase): The Follow-up Period consists of the Off-Tx Visit and the Follow-up Visits. The Off-Tx Visit will occur within 30 days following the last dose of study treatment. It applies to the Phase 1b subjects that discontinued study treatment early,

before completing Cycle 1, and to the Phase 2 subjects who discontinued study treatment early, before completing 8 cycles. Following the completion of the Off-Tx Visit, subjects will transition to the Follow-up Visits of the Extension Phase. The Follow-up Visits continue as long as the study subject is alive unless the subject withdraws consent or until the sponsor terminates the study. Subjects will be followed every 12 weeks (±1 week) for survival and subsequent anticancer treatments. The sponsor may decide to terminate survival follow-up anytime during the Extension Phase or when all subjects have discontinued study treatment.

Study Duration

Study duration for each subject is estimated to be:

- Pretreatment Phase: 4 weeks
- Treatment Phase:
    a. Phase 1b: 3 weeks (1 cycle)
    b. Phase 2: 24 weeks (8 cycles)
- Phase 1b and 2 Extension Phase: Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor termination of the study.

4 DETERMINATION OF SAMPLE SIZE

Phase 1b – Determination of the Maximum Tolerated Dose

The total number of subjects required for the Phase 1b portion of this study will depend upon the toxicities observed as the study progresses. A sample size of approximately 10 to 30 subjects in Phase 1b will be enrolled to assess MTD. This is not based on statistical power considerations.

Phase 2 – Expansion in Selected Tumor Types

A sample size of 10 evaluable subjects will be enrolled per cohort, with the possibility of expansion to 20 evaluable subjects per cohort, depending on the evaluation by the sponsor and investigators of the efficacy and safety results observed with the initial 10 evaluable subjects in each cohort. For a reference of the precision of ORR estimates in all cohorts except the endometrial carcinoma and the renal cell carcinoma cohorts, the associated 2-sided 95% CIs for the ORR of 10% to 90% for both 10 subjects and 20 subjects, per cohort are provided in

Table 1. 2-sided 95% Confidence Interval for the ORR of 10% to 90% (10 subjects and 20 subjects).

Table 1. 2-sided 95% Confidence Interval for the ORR of 10% to 90% (10 subjects and 20 subjects)

ORR (N=10)	95% CI
10%	(0.003, 0.445)
20%	(0.025, 0.556)
30%	(0.067, 0.653)
40%	(0.122, 0.738)
50%	(0.187, 0.813)
60%	(0.262, 0.878)
70%	(0.348, 0.933)
80%	(0.444, 0.975)
90%	(0.555, 0.998)
ORR (N=20)	**95% CI**
10%	(0.012, 0.317)
20%	(0.057, 0.437)
30%	(0.119, 0.543)
40%	(0.191, 0.639)
50%	(0.272, 0.728)
60%	(0.361, 0.809)
70%	(0.457, 0.881)
80%	(0.563, 0.943)
90%	(0.683, 0.988)

CI = confidence interval, ORR = objective response rate.

The endometrial carcinoma cohort may be further expanded to approximately 120 evaluable subjects. The decision to expand enrollment will be based on the results of 2 interim analyses which will spend β=0.012 and β = 0.024 at the first and second interim analysis, respectively. Based on an assumption of H_0: 16% ORR and H_1: 34% ORR, at 2-sided $\alpha = 0.02$, this design will give 97% statistical power with 120 subjects. At the first interim analysis (N = 21), if there are more than 3 responses, then approximately 40 additional subjects will be enrolled. At the second interim analysis (N = 60), if there are more than 12 responses, approximately 60

additional subjects will be enrolled. If there are 12 or fewer responses, the sponsor may decide whether to expand enrollment based on clinical outcome, eg, ORR and DOR. If the expansion beyond 60 subjects does not happen, this design for the endometrial carcinoma cohort has approximately 86% power at 2-sided α= 0.02. The boundaries for the decision to expand enrollment in the endometrial cohort are presented in Table 2.

Table 2. Boundaries for the Decision to Expand Enrollment in the Endometrial Carcinoma Cohort

Analysis Number	Cumulative β Spent	Objective Response Rate	P-value
Interim Analysis 1 (N=21)	0.012	0.167	0.93
Interim Analysis 2 (N=60)	0.024	0.204	0.357
Final Analysis (N=120)	0.03	0.238	0.02

As of Amendment 6, the renal cell carcinoma cohort may be further expanded to approximately 120 evaluable subjects. The decision to expand enrollment will be based on the results of 2 interim analyses. The first interim analysis will take place when 22 subjects (11 treatment naïve and 11 previously treated without an anti-PD-1/PD-L1 mAb) have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 22), if there are more than 5 responses, then approximately 45 additional subjects will be enrolled. It is anticipated that the additional 45 subjects will consist of approximately 12 treatment naïve subjects enrolled under Amendment 05 and approximately 33 previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 mAb. The second interim analysis will include these 45 additional subjects and the 11 treatment naïve subjects included in the first interim analysis and will take place when these 56 subjects have sufficient follow-up to be evaluated for response. Table 3 shows the ORR estimates that are close to the minimum anticipated ORR of about 25% in subjects who had previously failed an anti-PD-1/PD-L1 treatment and about 60% in treatment naïve subjects, and the corresponding 95% CIs in the respective anticipated 33 and 23 subjects for the second interim analysis. At the second interim analysis, whether the previously treated renal cell carcinoma subset will be further expanded will be decided based on clinical review of both efficacy and safety data.

Table 3. Estimate and 2-sided 95% Confidence Interval of the ORR (RCC Subjects for the Second Interim Analysis)

33 subjects who had previously failed an anti-PD-1/PD-L1 therapy		
Number of responses	**Observed ORR**	**95% CI**
7	21.2%	(0.090, 0.389)
8	24.2%	(0.111, 0.423)
9	27.3%	(0.133, 0.455)
10	30.3%	(0.156, 0.487)
11	33.3%	(0.180, 0.518)
12	36.4%	(0.204, 0.549)
23 treatment naïve subjects		
Number of responses	**Observed ORR**	**95% CI**
13	56.5%	(0.345, 0.768)
14	60.9%	(0.385, 0.803)
15	65.2%	(0.427, 0.836)
16	69.6%	(0.471, 0.868)
17	73.9%	(0.516, 0.898)

CI = confidence interval, ORR = objective response rate.

5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using n, mean, standard deviation (SD), median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects. All data will focus on the following 4 parts. Part 1 will focus on Phase 1b including some Phase 2 data. Part 2-4 will specifically focus on the solid tumor cohorts for their safety and efficacy.

Phase 1b/2: Selected outputs (e.g., disposition, demographic and baseline and disease characteristics, study drug exposure, DLT, and adverse events) will be provided for phase 1b subjects. The overall summary of the corresponding Phase 2 data may be included for the presentation.

EC cohort: primarily the data will be summarized by MSI/MMR status (Non-MSI-H/pMMR, MSI-H/dMMR, Not Available) and for overall. Efficacy results will be summarized by PD-L1

status and by the number of previous anticancer regimens. The Phase 1b and Phase 2 data will be combined for the analyses. RCC cohort: Efficacy subgroup analyses may be presented by the number of previous anticancer regimens, by PD-L1 status, and by subjects who were previously treated with/without an anti-PD-1/PD-L1 therapy. The Phase 1b and Phase 2 data will be combined for the analyses, as appropriate.

Four other cohorts: each cohort will be summarized separately. The Phase 1b and Phase 2 data will be combined for the analyses, as appropriate.

5.1 Study Endpoints

5.1.1 Primary Endpoints

Primary Efficacy Endpoint for Phase 1b:

The primary objective of Phase 1b is to determine the DLTs, MTD, and to establish the RP2D.

Primary Efficacy Endpoint for Phase 2:

The primary objective of Phase 2 is to evaluate $ORR_{(Week\ 24)}$ in each of the cohorts using irRECIST. $ORR_{(Week\ 24)}$ is defined as the proportion of subjects who have the best overall response (BOR) of $CR_{(Week24)}$ or $PR_{(Week\ 24)}$ as of the Week 24 tumor assessment time point. Subjects who did not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate.

5.1.2 Secondary Endpoint(s)

The secondary efficacy endpoints will be ORR, PFS, OS, DCR, CBR, DOR and durable SD by irRECIST (Appendix 13.1) as appropriate. The secondary efficacy endpoints are defined as follows.

- **ORR** is defined as the proportion of subjects who have BOR of partial or complete response (PR + CR) at the time of data cut-off. Subjects who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate.
- **PFS** is defined as the time from the first dose date to the date of the first documentation of disease progression or death (whichever occurs first) using irRECIST, see Appendix 13.1. If a subject did not experience a disease progression or death, then the subject will be censored at the date of the last available tumor assessment.

- **OS** is measured from the start date of the treatment period until date of death from any cause. Subjects who are lost to follow-up and the subjects who are alive at the date of data cutoff will be censored at the date the subject was last known alive.
- **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).
- **DOR** is defined as the time from the date of the first documentation of the confirmed CR or PR (whichever occurs first) to the date of the disease progression objectively documented or death (whichever occurs first). If a subject had no record of disease progression or did not die before the data cut-off date , then the subject will be censored at the last available tumor assessment.
- **Durable SD rate** is defined as the proportion of subjects whose BOR is SD and the duration of SD is ≥23weeks.

The safety endpoints include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECGs, and echocardiogram/MUGA results including LVEF.

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

5.1.3 Exploratory Endpoints

The exploratory endpoints include:

- Tumor response endpoints based on modified RECIST 1.1 assessments
- Tumor response endpoints for the subjects in the endometrial and renal cell carcinoma analysis sets based on IIR assessments using both irRECIST, modified RECIST 1.1 and RECIST 1.1.
- To identify and explore blood and tumor biomarkers which correlate with clinical endpoints of this study including safety and efficacy.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The following analysis sets will be defined:

Safety Analysis Set will include all subjects who received any amount of study drug. This will be the analysis set for all safety evaluations.

Full Analysis Set (Intent-to-Treat [ITT] Analysis Set) will include all subjects who entered the study treatment period. Efficacy analyses will primarily be based on the Full Analysis Set. Efficacy analaysis will use FAS and the specific cohort analysis set for EC, RCC and other cohorts.

Endometrial Carcinoma Analysis Set will include all endometrial carcinoma subjects from Phase 1b and Phase 2.

Renal Cell Carcinoma Analysis Set will include all renal cell carcinoma subjects from Phase 1b and Phase 2.

Non-Small Cell Lung Cancer Analysis Set will include all non-small cell lung cancer subjects from Phase 1b and Phase 2.

Melanoma Analysis Set will include all melanoma subjects from Phase 1b and Phase 2.

Pharmacokinetic (PK) Analysis Set will include all subjects who have received at least one dose of lenvatinib and have evaluable lenvatinib concentration data.

Pharmacodynamic (PD) Analysis Set will include all subjects who have received at least 1 dose of study drug (lenvatinib or pembrolizumab) and have evaluable pharmacodynamic data.

MTD Analysis Set will include all subjects who have completed cycle 1 treatment of Phase 1b or discontinued early due to DLT. This will be the analysis set to determine MTD.

5.2.2 Subject Disposition

The number and percent of enrolled and treated subjects who were on treatment, and those who discontinued study treatment at the time of the data cut-off will be summarized. The subjects who discontinued study treatment will be tabulated according to the primary reason for discontinuation. The end of study status (e.g., alive, death, withdrew consent, or lost to follow-up) at the data cutoff will also be summarized using the data from the survival follow-up eCRF.

5.2.3 Protocol Deviations

All protocol deviations will be determined prior to database lock and will be agreed upon by a review of individual subject data. This review will be undertaken in collaboration between the Study Director, the Study Statistician, the Study Data Manager and the Study Clinical Operations Manager.

5.2.4 Demographic and Other Baseline Characteristics

The demographics and baseline characteristics, including disease history and prior therapy, will be summarized using descriptive statistics.

- Demographic and other baseline characteristics will be summarized using the Full Analysis Set. For continuous demographic/baseline variables including age (year), height (cm), weight (kg) and BMI (body mass index) (kg/m^2), results will be summarized and presented as n, mean, standard deviation, median, 25% percentile (Q1), 75% percentile (Q3), minimum and maximum values. For categorical variables, the number and percentage of subjects will be used. Categorical variables include age group (<65 years, >=65 years), gender, race (White, Black or African American, Japanese, Chinese, Other Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other), ethnicity (Hispanic or Latino, not Hispanic or Latino), ECOG performance status, and NYHA cardiac disease classification.

Previous anticancer therapies/medications will be summarized as follows:

- Number of prior regimen,
- Duration of last therapy,
- Best response of last anti-cancer therapy (complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE), not applicable (NA), unknown),
- Time from end of last therapy to first dose,
- Type of last prior therapy (adjuvant, neoadjuvant, metastatic, locally advanced, and unknown),
- Prior surgical procedure (yes, no),

- Time from last prior surgical procedure to first dose,
- Subjects with any prior radiotherapy,
- Radiotherapy site (lymph node [neck/thoracic/abdominal and pelvic/other], bone [skull/spine/thorax/pelvis/extremities], brain, visceral [colorectal mass, lung mass, liver mass, chest, abdomen/pelvis], skin [trunk, extremity, head and neck], musculoskeletal [soft tissue-trunk, extremity, head and neck], miscellaneous),
- Tumor lesion at the site progressed since radiotherapy (yes, no, not evaluated),
- Time from last radiotherapy to the first dose.

Other baseline and disease characteristics include:

- Programmed Cell Death Protein – Ligand 1 (PD-L1) status.
  For subjects with both screening and baseline PD-L1 assessments, PD-L1 Status (Pre-treatment) is based on the most recent biopsy (baseline) assessment. PD-L1 positive is determined using a provisional cutoff by IHC per an investigational version of the PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA, USA).
- FIGO (Fédération Internationale de Gynécologie Obstétrique) grade for endometrial carcinoma subjects.
- Histologic subtype
- Microsatellite instability (MSI) and/or DNA Mismatch Repair (MMR) will be assessed locally and/or centrally for endometrial carcinoma subjects. Overall MSI/MMR Status will be determined by taking the central assessment first if both central and local assessments were available, then taking MMR result if both MMR and MSI assessments were available.
- Karnofsky performance status (KPS) will be summarized for the renal cell carcinoma subjects.

Disease history and characteristics at study entry will include:

- Time since solid tumor diagnosis to date of the first dose (months),
- Tumor type (Non-small cell lung cancer, Renal cell carcinoma, Endometrial cancer, Urothelial cancer, Squamous cell carcinoma of the head and neck, Melanoma),

- Age at diagnosis (in years) summarized both as a continuous and categorical variable (<65, >=65),
- Pathological Tumor-node-metastasis (TNM) staging at diagnosis,
- Target lesions (lymph node [yes/no], non-lymph node [yes/no], and non-target lesions [yes/no] based on the measurable disease criteria at study entry.
- The known mutation status including EGFR, KRAS, NRAS, BRAF, ALK translocation, RET translocation, ROS1 translocation, c-MET, IDH-1, IDH-2, Ki-67, P53, PIK3CA and others.

A summary table and a subject data listing of medical history will be provided, including system organ class and preferred term; current medical condition; date of diagnosis, surgical procedure, or onset of symptoms; and end date/on-going.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO, Geneva, Switzerland) Drug Dictionary using the March 2016 version or later. The number (percent) of subjects who have taken prior and concomitant medications will be summarized on the Full Analysis Set, by Anatomical Therapeutic Chemical (ATC) Classification and WHO drug preferred term. Prior medications will be defined as medications that stopped prior to the first dose of study drug. Concomitant medications will be defined as medications that (1) have started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (2) have started on or after the date of the first dose of study drug up to 30 days following the last dose of study drug. A medication that cannot be determined as prior/concomitant/post-treatment due to missing/incomplete dates will be regarded as a concomitant medication. The summary of concomitant, including anti-hypertensive, anti-diarrheal and corticosteroid medications/therapies will be provided.

Prior anti-cancer therapies including anti-cancer medications, anti-cancer procedures and radiotherapy will be summarized and listed. Data listings will be provided for all prior and concomitant medications.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses in Phase 1b and Phase 2. Center will not be considered as a factor in the analysis.

5.3.2 Adjustments for Covariates

Not applicable.

5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

5.3.4 Handling of Missing Data, Drop-outs, and Outliers

For incomplete dates involving efficacy and safety data such as adverse events, concomitant medications, laboratory values, vital signs, electrocardiograms (ECGs) and echocardiogram/MUGA data, a conservative imputation will be used for calculation. The imputation rules will be specified in study analysis dataset specification with more details. For endpoints which determine the percentage of responders, patients with unknown response will be treated as non-responders.

5.4 Efficacy Analyses

Tumor response will be assessed by both immune-related RECIST (irRECIST) and modified version of RECIST 1.1 criteria (mRECIST 1.1) per investigator assessment, and by irRECIST, mRECIST 1.1 and RECIST 1.1 per independent imaging review. All efficacy analyses will be performed on the Full Analysis Set for the specific cohort analysis set for EC, RCC and other cohorts. Tabular summary of key features of the efficacy analyses is described in Appendix 12.5 (Summary of Efficacy Analyses). Tumor assessments and overall response to the treatment according to irRECIST are presented in Appendix 13.1.

The best overall response (BOR) is determined once all the data for the subject is known. For this study, a confirmation of complete responses or partial responses is required for both irRECIST and modified RECIST 1.1; and following irRECIST, a confirmation of progression due to a tumor burden is required unless it is per investigator's discretion if the subject was

clinically unstable. The confirmation assessments should be made ≥4 weeks later. The BOR is determined by sequentially checking two adjacent assessments with ≥4 weeks apart (and with a few special cases). As an example if a subject had a stable disease at the timepoint 1, a partial response at the timepoint 2, a complete response at the timepoint 3, and another complete response at the timepoint 4, then the BOR for this subject is complete response, which was confirmed at the timepoint 4.

To program the BOR per irRECIST: (1)the tumor response data collected via both irRECIST and mRECIST 1.1 CRFs will be used; (2) any further response assessments after the second PD (confirmed PD per irRECIST) identified under irRECIST should not be considered for the BOR determination, however they should be presented in the data listings; (3) all tumor assessments as long as the subjects did not start a new anti-cancer therapy should be considered; (4) if there are more than 1 consecutive missing tumor assessments, all assessments afterward should not be considered for the determination of BOR (also see Section 5.4.3 for PFS). The BOR per irRECIST is defined as follows. Table 4 lists general rules in the derivation of BOR with two consecutive tumor response results (with a few special cases, see Table 4).

- **CR**

To achieve BOR of CR, CR must be observed at two consecutive tumor assessment visits with at least 4 weeks apart before a PD or death (whichever occurs first). If complete responses at two consecutive tumor assessment visits were with less than 4 weeks, the confirmation of CR at the next assessment visit is required.

The documented start date of CR as the BOR is defined as the date of the initial CR that was confirmed at the next consecutive visit (≥4weeks after the initial CR response).

- **PR**

When BOR of CR is not achieved, BOR of PR can be achieved when the initial PR was confirmed by a PR or CR at the next consecutive visit (≥4weeks after the initial PR response). If the two PRs (or PR and then CR) happened at two consecutive tumor assessment visits within 4 weeks, the additional confirmation of the PR is needed.

The documented start date of PR as the BOR is defined as the date of the initial PR that was confirmed at the next consecutive visit (≥4weeks after the initial PR response).

- **PD**

Following irRECIST, subject may continue treatment at the investigator's discretion after the initial PD due to pseudo-progression, if the subject is clinically stable. If a repeating imaging assessment at ≥ 4 weeks after the initial PD was not done, this initial PD response will be considered as a real PD. However, if there was subsequent tumor assessment (≥ 4 weeks) that showed a CR, PR or SD, regularly scheduled imaging assessments should be continued. The BOR will be determined based on all tumor assessments. When a PD is identified and confirmed under irRECIST, any further response assessments after the first PD under irRECIST should not be considered to determine BOR and PFS (i.e. the assessments up to the first PD under irRECIST will be considered for BOR and PFS), however these further assessments should be presented in the data listings.

The documented start date of PD is defined as the date of the initial PD that was confirmed at the next consecutive visit (i.e. a consecutive PD was identified ≥4weeks after the initial PD response), or the date of the initial PD if a repeating imaging assessment was not done, or the date of the first PD identified during irRECIST evaluations.

- **UNK (Unknown)**

If the subject did not have a baseline tumor assessment, then BOR = UNK (Unknown).

- **NE (Not Evaluable)**

If the subject did not have a post-baseline tumor assessment, or the subject only had one post-baseline tumor assessment of an early SD (duration < 5 weeks) as the overall response, or post-baseline tumor assessments are not evaluable (i.e. recorded as 'NE' as overall responses via the CRF, maybe due to missing anatomy or poor image quality), then BOR = NE.

- **SD**

If the BOR is not a confirmed CR/PR, NE, Unknown or PD, then the BOR is stable disease (SD).

Table 4 General Rules Deriving BOR per irRECIST

Timepoint 1 Overall Response	Timepoint 2 (≥ 4 weeks since Timepoint 1) Overall Response	BOR
CR	CR	CR
CR	PR	SD if duration of SD ≥ 5 weeks, otherwise PD
CR	SD	SD if duration of SD ≥ 5 weeks, otherwise PD
CR	PD	SD if duration of SD ≥ 5 weeks, otherwise PD
CR	NE	SD if duration of SD ≥ 5 weeks, otherwise NE. In the special case, if CR is at the next timepoint after NE, BOR will be CR.
CR [a]		SD if duration of SD ≥ 5 weeks, otherwise NE
PR	CR [b]	PR
PR	PR	PR
PR	SD	SD. In the special case if PR or CR is at the next timepoint after SD, BOR will be PR.
PR	PD	SD if duration of SD ≥ 5 weeks, otherwise PD
PR	NE	SD if duration of SD ≥ 5 weeks, otherwise NE. In the special case, if PR or CR is at the next timepoint after NE, BOR will be PR.
PR [a]		SD if duration of SD ≥ 5 weeks, otherwise NE
SD	CR [b]	SD
SD	PR [b]	SD
SD	SD	SD
SD	PD	SD if duration of SD ≥ 5 weeks, otherwise PD
SD	NE	SD if duration of SD ≥ 5 weeks, otherwise NE
SD [a]		SD if duration of SD ≥ 5 weeks, otherwise NE
PD	CR [b]	SD if duration of SD ≥ 5 weeks, otherwise PD
PD	PR [b]	SD if duration of SD ≥ 5 weeks, otherwise PD
PD	SD	SD if duration of SD ≥ 5 weeks, otherwise PD
PD	PD	PD

PD	NE	PD
PD [a]		PD
NE	NE	NE
UNK	UNK	UNK (Unknown) if there was no a baseline tumor assessment.

[a] If this was the only tumor response assessment (e.g. study treatment was discontinued). [b] The subject should be followed for ≥ 4 weeks to confirm the CR/PR.

5.4.1 Primary Analysis for Phase 1b

The primary objective of Phase 1b is to determine the DLTs, MTD, and to establish the RP2D. The endpoint DLTs in Phase 1b will be summarized based on the MTD Analysis Set.

5.4.2 Primary Efficacy Analysis for Phase 2

The primary efficacy endpoint in Phase 2 is objective response rate as of Week 24 ($ORR_{(Week\ 24)}$) based on irRECIST . The primary efficacy analysis of ORR(Week 24) for each cohort may be performed based on the Full Analysis Set when all subjects in that cohort have completed 8 cycles of treatment, or discontinued early due to disease progression, unacceptable toxicity, consent withdrawn, or the study termination by the Sponsor. Estimated $ORR_{(Week\ 24)}$ and the exact 95% confidence intervals using the method of Clopper–Pearson will be presented.

5.4.3 Secondary Efficacy Analyses for Both Phase 1b and Phase 2

The following secondary efficacy analyses will be performed.

Objective Response Rate (ORR): The ORR is the proportion of patients achieving a best overall response of confirmed PR or CR at the time of data cutoff. Subjects who do not have a tumor response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate. The count and percentage for the ORR will be summarized. ORR and corresponding 95% CI based on exact binomial distribution will be estimated for each treatment cohort.

Progression-Free Survival (PFS): The PFS is defined as the time from the first study dose date to the date of first documentation of confirmed PD using irRECIST 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 adequate radiologic assessment. The PFS censoring rules in this SAP and definition of progression date follow the principles of the Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)". Due to the use of pembrolizumab, all tumor assessments up to the first PD identified under irRCIST are considered as long as the subjects did not start a new anti-cancer therapy. The date of radiological assessment is based on the date of scans performed for a time point. The date will be based on the time point required CT/MRI scans unless there is a new lesion on the bone scan(s) or brain scan(s) performed to ensure CR or PR, or on brain scan(s) performed to ensure CR. Table 5 shows the censoring rules for the derivation of PFS.

Table 5 Censoring rules for the derivation of 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	Date of last adequate radiologic assessment	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 at regular interval as defined in the protocol.
** More than one missed visit/adequate tumor assessment is defined as having the duration between the last adequate tumor assessment and death or PD being longer than 14 weeks - 1 day, which is 97 days (= ((6+1) x 2 x 7) – 1) for subjects on the every 6 week tumor assessment schedule in the first 8 cycles of treatment and 20 weeks - 1 day, which is 139 days (= ((9+1) x 2 x 7) – 1) 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.

- If the subject died within 97 days (14 weeks -1 day) following 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, 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, No. 7).

The distribution of PFS and time curve will be estimated using Kaplan–Meier method. Median time to PFS and 95% CI will be provided for each cohort. Three-month, 6-month, 9-month, and 12-month PFS rate will be estimated using the Kaplan–Meier method and corresponding 95% CIs will be provided.

Overall Survival (OS): OS is measured from the start date of the treatment phase until date of death from any cause. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has no record of death, then the data will be censored at the date the subject was last known to be alive, or the data cutoff date, whichever is earlier (see Table 6 for censoring rules). The distribution of OS and time curve will be estimated using Kaplan–Meier method. Median survival time and the corresponding 95% CI, survival rates at 12, 18, and 24 months, and corresponding 95% CIs will be estimated using Kaplan–Meier method for each treatment cohort.

Table 6 Censoring Rules for Overall Survival Endpoint

Situation	Event Date or Censoring	Outcome
Death during study	Date of death	Death
Death after data cut-off	Date of data cut-off	Censored
Subject still alive at data cut-off	Date of data cut-off	Censored

Situation	Event Date or Censoring	Outcome
Subject lost to follow-up before data cut-off	Date last known to be alive	Censored

Disease Control Rate (DCR): The DCR is the proportion of subjects who have BOR of CR or PR or SD (minimum duration from C1D1 to SD ≥5 weeks). The count and percentage with exact 95% CI for the DCR will be summarized.

Clinical Benefit Rate (CBR): The CBR is the proportion of subjects who have BOR of CR or PR or durable SD (duration of SD ≥23 weeks). The count and percentage with exact 95% CI for the CBR will be summarized.

Duration of Response (DOR): The DOR is defined as the time from the date of the first documentation of the confirmed CR or PR (whichever occurs first) to the date of the disease progression objectively documented or death (whichever occurs first). If a subject had no record of disease progression or did not die before the data cut-off date, then the subject will be censored at the last available tumor assessment. The distribution of DOR will be estimated using Kaplan–Meier Method. Median duration of response and 95% CI will be provided.

5.4.4 Exploratory Efficacy Analysis

The efficacy tumor response endpoints (eg, PR, CR, SD and PD) will be explored based on modified RECIST 1.1 and RECIST 1.1 assessments. Same as the irRECIST, (1) a confirmation of complete responses or partial responses is required; (2) all tumor assessments as long as the subjects did not start a new anti-cancer therapy should be considered; (3) if there are more than 1 consecutive missing tumor assessments, all assessments afterward should not be considered for the determination of BOR (also see Section 5.4.3 for PFS). However, different from irRECIST, a pseudoprogression is considered as a PD per the modified RECIST 1.1 and RECIST 1.1. Therefore, following the modified RECIST 1.1 and RECIST 1.1, any further tumor response assessments after the initial PD are not considered to determine BOR. For programming, only the tumor response data collected via the CRF of the modified RECIST 1.1 will be used. The general rules in the derivation of BOR with two consecutive tumor response results following the modified RECIST 1.1 and RECIST 1.1 are described in Table

7.

Table 7 General Rules Deriving BOR per modified RECIST 1.1 and RECIST 1.1

Timepoint 1 Overall Response	**Timepoint 2 (≥ 4 weeks since Timepoint 1) Overall Response**	**BOR**
CR	CR	CR
CR	PR	SD if duration of SD ≥ 5 weeks, otherwise PD
CR	SD	SD if duration of SD ≥ 5 weeks, otherwise PD
CR	PD	SD if duration of SD ≥ 5 weeks, otherwise PD
CR	NE	SD if duration of SD ≥ 5 weeks, otherwise NE. In the special case, if CR is after NE, BOR will be CR.
CR [a]		SD if duration of SD ≥ 5 weeks, otherwise NE
PR	CR [b]	PR
PR	PR	PR
PR	SD	SD. In the special case if PR or CR is after SD, BOR will be PR.
PR	PD	SD if duration of SD ≥ 5 weeks, otherwise PD
PR	NE	SD if duration of SD ≥ 5 weeks, otherwise NE. In the special case, if PR or CR is after NE, BOR will be PR.
PR [a]		SD if duration of SD ≥ 5 weeks, otherwise NE
SD	CR [b]	SD
SD	PR [b]	SD
SD	SD	SD
SD	PD	SD if duration of SD ≥ 5 weeks, otherwise PD
SD	NE	SD if duration of SD ≥ 5 weeks, otherwise NE
SD [a]		SD if duration of SD ≥ 5 weeks, otherwise NE
PD [c]		PD
NE	NE	NE

UNK	UNK	UNK (Unknown) if there was no a baseline tumor assessment.

[a] If this was the only tumor response assessment (e.g. study treatment was discontinued).
[b] The subjects should be followed for ≥ 4 weeks to confirm the CR/PR.
[c] There is no need to confirm this PD per the modified RECIST 1.1 and RECIST 1.1 (e.g. pseudo-progressions is considered as a PD).

5.4.5 Other Efficacy Analyses

No other efficacy analyses are planned for this study.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

To assess any drug–drug interaction between lenvatinib and pembrolizumab, the dose-normalized PK profile for lenvatinib in combination with pembrolizumab from this study will be compared graphically to that from patients with different types of tumor from completed studies receiving lenvatinib monotherapy. PK analyses will be performed on Pharmacokinetic Analysis Set. Scatter plot, box plot and descriptive statistics including n, mean, SD, percent coefficient of variation (% CV), geometric mean, median, minimum and maximum will be used to summarize lenvatinib concentration data. All PK data, which include the complete bioanalytical results, time and date of blood draws and study drug administration, will be presented in subject-by-subject listings.

5.5.2 Pharmacodynamic, Pharmacogenomic and Other Biomarker Analyses

The effect of lenvatinib-pembrolizumab combination therapy on soluble, tissue, genetic and/or imaging biomarkers will be summarized using descriptive statistics using the pharmacodynamic analysis set. A separate analysis plan will be developed for the biomarker analyses, and results will be reported separately.

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, will be presented using descriptive statistics (e.g., n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous variables; n (%) for categorical variables). Safety variables include treatment-

emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, and echocardiogram results including LVEF.

5.6.1 Extent of Exposure

Summary will be provided for duration of treatment, total dose per subject, dose intensity, relative dose intensity (received dose as percentage of planned dose per subject. All parameters for extent of exposure will be computed separately for lenvatinib and pembrolizumab.

The end date for lenvatinib will be imputed to the analysis cut-off date if the subject is still on treatment at the time of the data cut-off, and the dose will be imputed with the last dose recorded in the database for that subject. Duration of lenvatinib or pembrolizumab treatment is calculated as date of last dose – date of first dose + 1. Overall duration of treatment is defined as the duration between the earliest first dose start date of either medication and the latest last dose end date of either medication. For lenvatinib, total dose per subject, dose intensity (mg/day/subject), and received dose as percentage of planned dose persubject (Calculated as cumulative total dose divided by (planned starting daily dose x treatment duration in days)) will be summarized. Total (cumulative) dose per subject (mg) is defined as the sum of all doses actually taken by the subject. For pembrolizumab, dose Intensity (mg/IV administration) of pembrolizumab = Total dose received during the study/total number of IV administrations.

Number of subjects with dose reductions, dose interruptions, and time to first dose reduction will be summarized by counts and percent according to dose data.

To determine dose reduction and dose interruption, the incorrect doses that were taken by mistake should not be considered. Dose reduction refers to the situation that a dose level was reduced from the previous dose level without going back. Dose reduction is only applicable to lenvatinib, but not for Pembrolizumab as Pembrolizumab dose is always 200mg if it is administered. As an example below, the subject had two dose reductions on Day 4 and Day 6.

Obs	Subject Identifier	Treatment	Dose per Administration	Study Day of Start of Treatment	Study Day of End of Treatment
1	1001-10xx	LENVATINIB	20	1	2

2	1001-10xx	LENVATINIB	0	3	3
3	1001-10xx	LENVATINIB	14	4	5
4	1001-10xx	LENVATINIB	8	6	21
5	1001-10xx	LENVATINIB	8	22	50

Dose interruption for lenvatinib is defined as follow. The maximum days of dose interruptions is the duration of the longest interruption.

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

For Pembrolizumab, as long as a dose was administered for a cycle, then there is no an interruption for this cycle.

Number of subjects with drug discontinuations due to AEs will be summarized by frequency counts and percentages.

5.6.2 Dose Limiting Toxicity

Each subject in a dose level in Phase 1b is monitored every week by Eisai clinical team and the principal investigators or more frequently if necessary. DLTs are declared by both parties as well as the decisions to expand/continue or decrease the dose level cohort. The dose limiting toxicities will be presented.

5.6.3 Deaths, Serious and Other Significant Adverse Events

The adverse event verbatim descriptions (investigator terms from the eCRF) 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 primary System Organ Class (SOC) and preferred term (PT) using MedDRA.

A treatment-emergent adverse event (TEAE) is defined as an adverse event that had an onset date, or a worsening in severity from baseline (pre-treatment), on or after the first dose of study drug up to the last visit, or 30 days following the last dose of study drug. In addition, if an AE reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, it is also counted as a TEAE. Due to the use of pembrolizumab, serious adverse events (SAEs) occurring up to 90 days after the last dose of study drug will be considered as treatment-emergent serious adverse events.

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

The incidence of TEAEs will be reported as the number (percent) of subjects with TEAEs within SOC and PT. Subjects will be counted only once within a SOC and PT. If the subject experienced more than one TEAE within a specific SOC and PT, the subject will be counted with the worst grade for that AE. The number (percent) of subjects with TEAEs will also be summarized by highest Common Terminology Criteria for Adverse Events (CTCAE) grade. In summary, the following TEAE tables will be provided:

- Overview of TEAEs.
- TEAEs by SOC, PT, and CTCAE grade.
- TEAEs with CTCAE grade >=3
- TEAE with outcome of death.
- Treatment-related TEAEs by SOC, PT, and CTCAE grade
- Treatment-related TEAEs with CTCAE grade >=3
- Treatment-related TEAEs with outcome of death

The following subject AE listings (regardless treatment emergent or not) will be provided:

- All adverse events.

A subject data listing of all deaths will be provided with the information of primary reasons of deaths, deaths within 30 days of last dose, deaths > 30 days of last dose, and treatment-related deaths.

The number (percent) of subjects with treatment-emergent serious adverse events will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided. The number (percent) of subjects with TEAEs leading to discontinuation, dose reduction, or dose interruption from study treatment will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation, dose modification, or dose interruption from study treatment will be provided. In summary, the following TEAE tables will be provided:

- SAEs
- Treatment related SAEs
- TEAEs leading to study drug dose interruption by SOC and PT.
- TEAEs leading to study drug dose reduction by SOC and PT.
- TEAEs leading to study drug discontinuation by SOC and PT.
- Clinically significant TEAEs (CSAE) for lenvatinib, by PT and CTCAE grade (any grade vs ≥ 3).
- TEAEs of special interest (AEOSI) for pembrolizumab, by PT and CTCAE grade (any grade vs ≥ 3).

The following subject AE listings (treatment emergent or not) will be provided:

- All deaths for all enrolled subjects.
- All serious adverse events (SAEs).
- All fatal TEAE
- All AEs leading to dose interruption
- All AEs leading to dose reduction.
- All AEs leading to study drug discontinuation.

5.6.4 Laboratory Values

Laboratory values that are non-missing and reported as 'below the detectable limit' of an assay will be replaced by half the detectable limit in the summary tables. Laboratory results will be summarized using the S*ystème international* (SI) units. Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Abnormal laboratory values will be identified as those outside the normal range. The abnormal values will be indicated in data listings. Laboratory parameters will also be categorized according to CTCAE v4.03 grades, and shifts from baseline CTCAE grades to worst grades will be assessed.

For quantitative parameters, the actual value and the change from baseline to each post-baseline visit, will be summarized by visit using descriptive statistics if needed. Urinalysis parameters (qualitative) will be listed.

Only laboratory parameters specified in the protocol will be summarized. Other laboratory parameters collected for some individual subjects will be presented in listings.

5.6.5 Vital Signs

Vital sign values will be evaluated on an individual basis by subject. Descriptive statistics for vital signs parameters (diastolic and systolic blood pressure, resting HR, respiratory rate, body temperature, and weight) and changes from baseline will be presented.

5.6.6 Electrocardiograms

Electrocardiogram (ECG) assessments will be performed at screening and at Day 1 of each cycle. Descriptive statistics for electrocardiogram parameters (HR, PR, QRS, QT, QTcB, QTcF and RR) and changes from baseline will be presented by visit. ECG findings (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) will be summarized using shift tables. A subject data listing will also be provided.

5.6.7 Other Safety Analyses

Left ventricular ejection fraction (LVEF) obtained on echocardiogram or MUGA scans will be summarized with descriptive statistics for baseline and post-baseline lowest value. Percent change of the post-baseline lowest value from baseline will be presented. A subject data listing

will be provided.

5.7 Exploratory Analyses

The exploratory analyses as described in Section 5.5 (Pharmacokinetic, Pharmacodynamic, Pharmacogenomic and Other Biomarker Analyses) will be reported separately from the clinical study report.

6 INTERIM ANALYSES

The evaluation of efficacy and safety by the sponsor and investigators will occur on the initial 10 evaluable subjects while enrollment is ongoing. Based on the outcome of the evaluation the enrollment could be suspended before enrolling the planned 20 subjects in each cohort.

The endometrial carcinoma cohort may be expanded to approximately 120 evaluable subjects. Two interim analyses will take place when 21 and 60 subjects have sufficient follow-up to be evaluated for response. The decision to expand enrollment will be based on the results of the 2 interim analyses, which will spend β= 0.012 and β= 0.024 at the first and second interim analyses, respectively. Based on an assumption of H_0: 16% ORR and H_1: 34% ORR, at 2-sided α = 0.02, this design will give 97% statistical power with 120 subjects. At the first interim analysis (N = 21), if there are more than 3 responses, then approximately 40 additional subjects will be enrolled. At the second interim analysis (N = 60), if there are more than 12 responses, approximately 60 additional subjects will be enrolled. If there are 12 or fewer responses, the sponsor may decide whether to expand enrollment based on clinical outcome, eg, ORR and DOR. If the expansion beyond 60 subjects does not happen, this design for the endometrial carcinoma cohort has approximately 86% power at 2-sided α = 0.02.

The renal cell carcinoma cohort may be further expanded to approximately 120 evaluable subjects. The decision to expand enrollment will be based on the results of 2 interim analyses. The first interim analysis will take place when 22 subjects (11 treatment naïve and 11 previously treated without an anti-PD-1/PD-L1 therapy) have sufficient follow-up to be evaluated for response. At the first interim analysis (N = 22), if there are more than 5 responses, then approximately 45 additional subjects will be enrolled. It is anticipated that the additional

45 subjects will consist of approximately 12 treatment naïve subjects enrolled under Amendment 05 and approximately 33 previously treated subjects who have received 1 or 2 prior therapies and have progressed on treatment with an anti-PD-1/PD-L1 mAb. The second interim analysis will include these 45 additional subjects and the 11 treatment naïve subjects included in the first interim analysis and will take place when these 56 subjects have sufficient follow-up to be evaluated for response. At the second interim analysis, whether the previously treated renal cell carcinoma subset will be further expanded will be decided based on clinical review of both efficacy and safety data.

7 CHANGES IN THE PLANNED ANALYSES

Not applicable.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

Study Day 1

Study Day 1 is defined as the day of the first dose of study drug administered.

Baseline

Baseline is defined as a Day 1 pre-dose, the last observation before the start of drug, if the Day 1 pre-dose is missing.

By-visit analyses

All by-visit analyses will be performed using assessments at corresponding scheduled visits recorded in the eCRF. For shift tables, all post-baseline assessments including those at scheduled and unscheduled visits will be used.

Incomplete dates

For incomplete dates involving efficacy and safety data, see Section 5.3.4 for data handlings.

Limit of Quantification (BLQ) in pharmacokinetics analyses

When calculating the mean or median value for the concentrations at a given time point, the BLQ values will be assigned as zero. If the proportion of values reported as BLQ is more than 50%, no summary statistics should be represented at that time point, and the value will be treated as missing in mean or median concentration profiles.

More specific details, if any, are given with the discussion of analyses for each endpoint. Details on the way that BLQ values will be replaced will be described in a separate plan detailing the analyses.

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

Statistical programming and analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9 or higher, and/or other validated statistical software as required.

11 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

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

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13 APPENDICES

13.1 Immune-Related Response Evaluation Criteria In Solid Tumors (irRECIST)

Investigators should follow the guidelines provided here which are an adaptation of RECIST 1.1 and immune-related response criteria (irRC). The following guide represents a summary of irRECIST and is meant to help investigators in providing more objective and reproducible immune therapy related tumor response assessments in solid tumors.

The key changes for irRECIST are:

- In contrast to RECIST 1.1, irRECIST allows the site to select up to ten (10) target lesions at baseline, five (5) per organ, if clinically relevant via CT/MRI scans or by electronic calipers for skin lesions. The ability to continue treatment, if clinically stable, until repeat imaging scans ≥ 4 weeks later (in most cases at the next scanning time point 6 weeks later) to confirm Progressive Disease (PD)

irRECIST Lexicon	
1. Baseline Assessments	
Measurable (Target) lesions	Measurable lesions must be accurately measured in at least one dimension with a minimum size of: • 10 mm in the longest diameter (LDi) by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis (SDi) for nodal lesions • 10 mm in LDi for clinical lesions (must be measured using electronic calipers) • Identify up to 10 lesions, not more than 5 from one organ system. Lymph nodes are considered one organ system • Likely to be reproducible across all time points • Representative of tumor burden • May include lesions in previously irradiated areas ONLY if there is demonstrated progression in that lesion after irradiation • Sum of diameters (SOD) of all target lesions including nodal and non-nodal are reported as baseline SOD which is used for assessing tumor response at follow-up time points
Bone lesions	Regardless of the imaging modality, blastic bone lesions will **not be** selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.

Cystic and Necrotic Lesions as Target Lesions	Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the SOD of all target lesions at baseline. If other lesions with a nonliquid/nonnecrotic component are present, those should be preferred.
Lesions with Prior Local Treatment	During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progression in the lesion.
Nonmeasurable (Non-Target) lesions	Non-target lesions will include: • Measurable lesions not selected as target lesions. There is no limit to the number of non-target lesions that can be recorded at baseline • Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc. • Multiple non-target lesions from the same organ may be captured as a single item on the eCRF (e.g. multiple liver metastases) Non-target lesions should be reported as present at baseline
$SOD_{baseline}$	Sum of diameters at baseline = LDi of all non-nodal + SDi of all nodal target lesions
2. Time Point Assessments After Baseline	
Target lesion measurements	Locate image that optimizes the LDi of the non-nodal target lesion or short axis of target node(s). There is no need to go to an identical slice from baseline. Measure the respective LDi and SDi for all target lesions and calculate time point SOD ($SOD_{timepoint}$). Special consideration for target lesions: • If target lesion is too small to measure, a default value of 5mm should be entered on eCRF. • If target lesion is 5-10mm, actual diameter should be entered in the eCRF • If target lesion splits into 2 or more lesion then the LDi of split lesions will be added and entered in place of that lesion • If two target lesion merged to form one lesion than LDi of one should be entered as “0mm” while the other lesion should have the diameter of the merged lesion

Nontarget Lesion Assessment	Nontarget lesions are evaluated qualitatively as present, absent, not evaluable (NE) or unequivocal progression. The response of nontarget lesions primarily contributes to the overall response assessments of CR. Nontarget lesions do not affect PR and SD assessments. Only a massive and unequivocal worsening of nontarget lesions alone, even in the presence of stable disease or a partial response in the target lesion is indicative of PD. CR is not possible unless all non-target lesions are absent.
Definition of New lesion	Any lesion which was not recorded at baseline. There is no minimum size criteria to identify a new lesion and clinical judgment must be used by the PI. • May include a lesion in an anatomical location that was not scanned at baseline (i.e. brain) • Should be unequivocal and not due to differences in scanning technique • If equivocal, should be assessed at next timepoint; if present, PD is the date the lesion was first seen (not the date confirmed)
3. irRECIST Overall Tumor Assessment	
CR	• Complete disappearance of all measurable and nonmeasurable lesions (from baseline) and there are no unequivocal new lesions (unconfirmed CR). • Lymph nodes must decrease to < 10 mm in short axis. • Confirmation of response is required ≥ 4 weeks later, preferably at next time point, to be considered a confirmed CR.
PR	• If the **$SOD_{timepoint}$ of TLs decreases by ≥ 30 % compared to $SOD_{baseline}$** and there are no unequivocal new lesions, and no progression of nontarget disease, it is an PR (unconfirmed). • Confirmation is required ≥ 4 weeks later, preferably at next time point, to be considered a confirmed PR.
SD	Failure to meet criteria for CR or PR in the absence of PD. • If the sum of the TLs and the status of the nontarget lesions do not reach the criteria to meet PR or PD (increase ≥20% and at least 5 mm absolute increase in SOD compared to nadir†) the response is SD. • **SD = neither 30% decrease compared to $SOD_{baseline}$ or 20% increase and at least 5 mm absolute change compared to nadir.** • **†SOD_{nadir}:** Lowest measure SOD of TLs at any time point from baseline onward.
PD	Minimum 20% increase and a minimum 5 mm absolute increase in SOD compared to nadir, or PD for nontarget lesion(s) or unequivocal new lesion(s).

- Confirmation of progression is recommended at a minimum of 4 weeks after the first PD assessment (preferably at next tumor assessment time point).

The decision to continue study treatment after the first evidence of PD is at the Investigator's discretion based on the clinical status of the subject as described in table below

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks (next TA time point) to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scans	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Subsequent scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Subsequent scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

Subjects may continue receiving study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

	• Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression • No decline in ECOG performance status • Absence of rapid progression of disease • Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention If PD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact Sponsor to discuss continuing treatment
NE	Used in exceptional cases where insufficient data exists due to poor quality of scans or missed scans or procedure

Derivation of irRECIST overall responses			
Measurable response	Nonmeasureable response		
Target Lesions (% change in SOD)*	Non-Target Lesions Status	New Lesions Status	Overall Response (irRECIST)
↓100	Absent	Absent	CR¥
↓100	Present/NE	Absent	PR¥
↓≥30	Present/Absent/NE	Absent	PR¥
↓<30 to <20↑	Present/Absent/NE	Absent	SD
↓100 ↓≥30 ↓<30 to <20↑ NE	Present/Absent/NE	Present	PD¥
↓100 ↓≥30 ↓<30 to <20↑ NE	Unequivocal progression	Any	PD¥
↑≥20 from nadir	Any	Any	PD¥
NE	Present/Absent/NE	Absent	NE¥

* Decreases assessed relative to baseline, including measureable lesions only.

¥ Assuming response (CR and PR) and progression (PD) are confirmed by a second, consecutive assessment at least 4 week apart.

13.2 Dose-Limiting Toxicities

A Dose-limiting toxicity (DLT) is defined as any of the following as judged by the investigator.

- Any of the hematological or nonhematological toxicities noted in the table below considered to be at least possibly related to lenvatinib and/or pembrolizumab occurring during Cycle 1.
- Failure to administer ≥75% of the planned dosage of lenvatinib as a result of treatment-related toxicity during Cycle 1.
- Subjects who discontinue treatment due to treatment-related toxicity.
- Greater than 2 week delay in starting Cycle 2 because of a treatment-related toxicity, even if the toxicity does not meet DLT criteria.

Dose Limiting Toxicities	
Toxicity Category	Toxicity CTCAE Grade
Hematologic	Grade 4 neutropenia for ≥7 days
	Grade 3 or Grade 4 febrile neutropenia[a]
	Thrombocytopenia <25,000/mm^3 associated with bleeding and/or that requires platelet transfusion
Other nonhematologic toxicity	Any other Grade 4 or a Grade 5 toxicity Grade 3 toxicities lasting >3 days excluding: Nausea, vomiting, and diarrhea controlled by medical intervention within 72 hours. Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab.
	Grade 3 hypertension not able to be controlled by medication
	Grade 3 or above gastrointestinal perforation
	Grade 3 or above wound dehiscence requiring medical or surgical intervention
	Any grade thromboembolic event

	Any Grade 3 nonhematologic laboratory value if: Medical intervention is required to treat the subject, or the abnormality leads to hospitalization
ANC = absolute neutrophil count, CTCAE = Common Terminology Criteria for Adverse Events v4.03. a. Febrile neutropenia Grade 3 or Grade 4: Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour. Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour, with life-threatening consequences and urgent intervention indicated	

Only toxicities with a clear alternative explanation (eg, due to disease progression) or transient (≤72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination can be deemed a non-DLT.

All subjects enrolled in Phase 1b will be assessed for DLTs during the DLT assessment window of Cycle 1 (Treatment Phase). Subjects who discontinue study treatment prior to completing the Treatment Phase for any reason other than DLT will be replaced. Once they complete the Treatment Phase, each subject still receiving study treatment will transition into the Extension Phase. Tumor assessments will continue during the Extension Phase.

13.3 Common Terminology Criteria For Adverse Events (CTCAE) V4.03

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

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

Grade	CTCAE Status

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

ADL = activities of daily living, CTCAE = Common Terminology Criteria for Adverse Events.
a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.03

For further details regarding MedDRA, refer to the MedDRA website at:

http://www.meddramsso.com

13.4 New York Heart Association (NYHA) Cardiac Disease Classification

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

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

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

13.5 Summary of primary and secondary Efficacy Analyses

Based on investigator assessments per irRECIST and mRECIST 1.1 for all 6 tumor cohorts, the following will be included in he efficacy analysis on the full analysis set or tumor specific analysis sets.

Efficacy Variable	Statistical Method
$ORR_{(Week\ 24)}$	Number (percent) of subjects (with PR + CR) at Week 24 and its exact 95% CI using method of Clopper-Pearson. (Only for irRECSIT)
ORR	Number (percent) of subjects (with PR + CR) and its exact 95% CI using method of Clopper-Pearson.
PFS	Kaplan-Meier method: Median PFS, and progression-free survival rate at 3, 6, 9, and 12 months will be presented with 2-sided 95% CIs. Kaplan-Meier plot will also be provided.
OS*	Kaplan-Meier method: Median OS, and survival rates at 12, 18, and 24 months will be presented with 2-sided 95% CIs. Kaplan-Meier plot will also be provided.
DCR	Number (percent) of subjects (with CR + PR + stable disease [SD] ≥ 5 weeks) and its exact 95% CI using method of Clopper-Pearson.
CBR	Number (percent) of subjects (with CR, PR + durable SD≥23 weeks) and its exact 95% CI using method of Clopper-Pearson.
DOR	Kaplan-Meier method: Median DOR with 2-sided 95% CIs will be presented.

* The OS endpoint is independent from tumor assessment criteria.

Based on independent imaging review per irRECIST, mRECIST 1.1, RECIST 1.1 for EC and RCC cohorts, the following will be included in efficacy analyses on the Endometrial Carcinoma Analysis Set and Renal Cell Carcinoma Analysis Set.

Efficacy Variable	Statistical Method
$ORR_{(Week\ 24)}$	Number (percent) of subjects (with PR + CR) at Week 24 and its exact 95% CI using method of Clopper-Pearson. (Only for irRECIST)
ORR	Number (percent) of subjects (with PR + CR) and its exact 95% CI using method of Clopper-Pearson.
PFS	Kaplan-Meier method: Median PFS, and progression-free survival rate at 3, 6, 9, and 12 months will be presented with 2-sided 95% CIs. Kaplan-Meier plot will also be provided.
DCR	Number (percent) of subjects (with CR + PR + stable disease [SD] ≥ 5 weeks) and its exact 95% CI using method of Clopper-Pearson.
CBR	Number (percent) of subjects (with CR, PR + durable SD≥23 weeks) and its exact 95% CI using method of Clopper-Pearson.
DOR	Kaplan-Meier method: Median DOR with 2-sided 95% CIs will be presented.

13.6 Common Terminology Criteria for Adverse Events (CTCAE) for Hematology & Clinical Chemistry

Laboratory Parameter	Common Terminology Criteria for Adverse Events (CTCAE)			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
		Hematology		
Hemoglobin	< LLN – 10 *g/d*L < LLN – 6.2 *mmol*/L	< 10 – 8 *g/d*L < 6.2 – 4.9 *mmol*/L	< 8 – 6.5 *g/d*L < 4.9 – 4 *mmol*/L	–
Platelet Count	< LLN – 75,000/mm^3 < LLN – 75 x 10^9/L	< 75,000 – 50,000/mm^3 < 75 – 50 x 10^9/L	< 50,000 – 25,000/mm^3 < 50 – 25 x 10^9/L	< 25,000/mm^3 < 25 x 10^9/L
Leukocytes (Total WBC)	< LLN – 3,000/mm^3 < LLN – 3 x 10^9/L	< 3,000 – 2,000/mm^3 < 3 – 2 x 10^9/L	< 2,000 – 1000/mm^3 < 2 – 1 x 10^9/L	< 1,000/mm^3 < 1 x 10^9/L
Lymphocytes (*hypo*)	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L

Laboratory Parameter	Common Terminology Criteria for Adverse Events (CTCAE)			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lymphocytes (*hyper*)	-	> 4,000 – 20,000/mm^3 > 4 – 20 x 10^9/L	> 20,000/mm^3 > 20 x 10^9/L	–
Neutrophils	< LLN – 1,500/mm^3 < LLN – 1.5 x 10^9/L	< 1,500 – 1,000/mm^3 < 1.5 – 1 x 10^9/L	< 1,000 – 500/mm^3 < 1 – 0.5 x 10^9/L	< 500/mm^3 < 0.5 x 10^9/L
		Clinical Chemistry		
Albumin	< LLN – 3 *g*/*d*L < LLN – 30 *g*/L	< 3 – 2 *g*/*d*L < 30 – 20 *g*/L	< 2 *g*/*d*L < 20 *g*/L	
Alkaline Phosphatase	> 1 – ≤ 2.5 x ULN	> 2.5 – ≤ 5 x ULN	> 5 – ≤ 20 x ULN	> 20 x ULN
ALT	> 1 – ≤ 3 x ULN	> 3 – ≤ 5 x ULN	> 5 – ≤ 20 x ULN	> 20 x ULN
Amylase	> 1 – ≤ 1.5 x ULN	> 1.5 – ≤ 2 x ULN	> 2 – ≤ 5 x ULN	> 5 x ULN
AST	> 1 – ≤ 3 x ULN	> 3 – ≤ 5 x ULN	> 5 – ≤ 20 x ULN	> 20 x ULN
Bilirubin, Total	> 1 – ≤ 1.5 x ULN	> 1.5 – ≤ 3 x ULN	> 3 – ≤ 10 x ULN	> 10 x ULN
Calcium (*hyper*)	> ULN – ≤ 11.5 *mg*/*d*L > ULN – ≤ 2.9 *mmol*/L	> 11.5 – ≤ 12.5 *mg*/*d*L > 2.9 – ≤ 3.1 *mmol*/L	> 12.5 – ≤ 13.5 *mg*/*d*L > 3.1 – ≤ 3.4 *mmol*/L	> 13.5 *mg*/*d*L > 3.4 *mmol*/L
Calcium (*hypo*)	< LLN – 8 *mg*/*d*L < LLN – 2 *mmol*/L	< 8 – 7 *mg*/*d*L < 2 – 1.75 *mmol*/L	< 7 – 6 *mg*/*d*L < 1.75 – 1.5 *mmol*/L	< 6 *mg*/*d*L < 1.5 *mmol*/L
Cholesterol, Total	> ULN – 300 *mg*/*d*L > ULN – 7.75 *mmol*/L	> 300 – 400 *mg*/*d*L > 7.75 – 10.34 *mmol*/L	> 400 – 500 *mg*/*d*L > 10.34 – 12.92 *mmol*/L	> 500 *mg*/*d*L > 12.92 *mmol*/L
Creatinine	> 1 – ≤ 1.5 x ULN	> 1.5 – ≤ 3 x ULN	> 3 – ≤ 6 x ULN	> 6 x ULN
Glucose (*hyper*)	> ULN – ≤ 160 *mg*/*d*L > ULN – ≤ 8.9 *mmol*/L	> 160 – ≤ 250 *mg*/*d*L > 8.9 – ≤ 13.9 *mmol*/L	> 250 – ≤ 500 *mg*/*d*L > 13.9 – ≤ 27.8 *mmol*/L	> 500 *mg*/*d*L > 27.8 *mmol*/L
Glucose (*hypo*)	< LLN – 55 *mg*/*d*L < LLN – 3 *mmol*/L	< 55 – 40 *mg*/dL < 3 – 2.2 *mmol*/L	< 40 – 30 *mg*/*d*L < 2.2 – 1.7 *mmol*/L	< 30 *mg*/*d*L < 1.7 *mmol*/L
Lipase	> 1 – 1.5 x ULN	> 1.5 – ≤ 2 x ULN	> 2 – 5 x ULN	> 5 x ULN
Magnesium (*hyper*)	> ULN – ≤ 3 *mg*/*d*L > ULN – ≤ 1.23 *mmol*/L	–	> 3 – ≤ 8 *mg*/*d*L > 1.23 – ≤ 3.3 *mmol*/L	> 8 *mg*/*d*L > 3.3 *mmol*/L

Laboratory Parameter	Common Terminology Criteria for Adverse Events (CTCAE)			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Magnesium (*hypo*)	< LLN – 1.2 *mg*/*d*L < LLN – 0.5 *mmol*/L	< 1.2 – 0.9 *mg*/*d*L < 0.5 – 0.4 *mmol*/L	< 0.9 – 0.7 *mg*/*d*L < 0.4 – 0.3 *mmol*/L	< 0.7 *mg*/*d*L < 0.3 *mmol*/L
Phosphate	< LLN – 2.5 *mg*/dL < LLN – 0.8 *mmol*/L	< 2.5 – 2 *mg*/*d*L < 0.8 – 0.6 *mmol*/L	< 2 – 1 *mg*/*d*L < 0.6 – 0.3 *mmol*/L	< 1 *mg*/*d*L < 0.3 *mmol*/L
Potassium (*hyper*)	> ULN – ≤ 5.5 *mmol*/L	> 5.5 – ≤ 6 *mmol*/L	> 6 – ≤ 7 *mmol*/L	> 7 *mmol*/L
Potassium (*hypo*)	< LLN – 3 *mmol*/L	–	< 3 – 2.5 *mmol*/L	< 2.5 *mmol*/L
Sodium (*hyper*)	> ULN – ≤ 150 *mmol*/L	> 150 – ≤ 155 *mmol*/L	> 155 – ≤ 160 *mmol*/L	> 160 *mmol*/L
Sodium (*hypo*)	< LLN – 130 *mmol*/L	–	< 130 – 120 *mmol*/L	< 120 *mmol*/L

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