STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7386-G000-201
Study Protocol Title:	An Open-Label, Multicenter, Phase 1b/2 Study of E7386 in Combination With Pembrolizumab in Previously Treated Subjects With Selected Solid Tumors
Date:	26 Jun 2024
Version:	Version 1.0

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
β-CTX	beta-C-terminal telopeptide
BID	twice daily
BOR	best overall response
CR	complete response
CBR	clinical benefit rate
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECOG PS	Eastern Cooperative Oncology Group (ECOG) Performance Status
HCC	hepatocellular carcinoma
IV	intravenous(ly)
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
ORR	objective response rate
OS	overall survival
P1NP	procollagen type 1 N-terminal propeptide
PD	pharmacodynamic
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumours

Abbreviation	Term
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TEAE	treatment-emergent adverse event
WHO	World Health Organization

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 the Eisai protocol for Study E7386-G000-201 (Amendment 04.1). CCI [redacted]

3.1 Study Objectives

3.1.1 Primary Objectives

Phase 1b part:

- To assess the safety and tolerability of E7386 in combination with pembrolizumab in subjects with previously treated selected solid tumors
- To determine the recommended Phase 2 dose (RP2D) of E7386 in combination with pembrolizumab

Phase 2 part:

- To assess the objective response rate (ORR) of E7386 in combination with pembrolizumab (melanoma, colorectal cancer [CRC], hepatocellular carcinoma [HCC]) according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

3.1.2 Secondary Objectives

Phase 1b part only:

- To assess tumor response according to RECIST 1.1

Phase 1b and Phase 2 parts:

- To assess duration of response (DOR) according to RECIST 1.1 per tumor cohort
- To assess the disease control rate (DCR: the proportion of subjects with complete response [CR], partial response [PR], or stable disease [SD] after ≥5 weeks from the first dose) according to RECIST 1.1 per tumor cohort
- To assess the clinical benefit rate (CBR: the proportion of subjects with CR, PR, or durable SD [duration of SD ≥23 weeks]) according to RECIST 1.1 per tumor cohort
- To assess the safety and tolerability of E7386 in combination with pembrolizumab
- To evaluate the pharmacokinetic (PK) profile of E7386 when co-administered with pembrolizumab

3.1.3 Exploratory Objectives

Phase 1b and Phase 2 parts:

[redacted]

[redacted]

3.2 Overall Study Design and Plan

This is an open-label, multicenter, Phase 1b/2 study that will evaluate the safety and efficacy of E7386 in combination with pembrolizumab. CCI [redacted] Safety, tumor response, PK, and PD assessments will be performed on every subject; details are described in the Schedule of Procedures/Assessments in the study protocol Section 9.5.2.

The study is divided into 3 parts (Phase 1b part, Phase 2 part, and Extension part), and each part will be conducted in 3 phases: Pretreatment Phase (including Screening Period and Baseline Period), Treatment Phase, and Follow-Up Phase (after the End of Treatment [EOT]).

Eligible subjects will be enrolled into 1 of 3 tumor cohorts: melanoma, CRC, and HCC.

Study design details are included in the study protocol Section 9.1.

4 DETERMINATION OF SAMPLE SIZE

Phase 1 b part, Dose Escalation

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Phase 2 part, Dose Expansion (E7386 Plus Pembrolizumab Cohorts)

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5 STATISTICAL METHODS

Statistical analyses will be performed by the sponsor or designee after the data cutoff and the database is locked and released. An earlier database lock may also be performed for the purpose of writing a clinical study report (CSR). Statistical analyses will be performed using SAS software or other validated statistical software, as required.

Data cutoff for the primary analyses in the Phase 2 part for each tumor cohort will be performed based on the Efficacy Analysis Set when all subjects have a tumor assessment

until [redacted] and/or have adequate follow-up to be evaluated for DOR, or they have discontinued early due to any cause. The full final analysis will be performed after all subjects complete from the study.

All descriptive statistics for continuous variables will be reported using mean, standard deviation, median, first quantile (Q1), third quantile (Q3), minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

For the tumor response related endpoints, the tumor assessments by blinded independent central review (BICR) (if conducted) may be used in the primary analysis for the cohorts in Phase 2 part. Otherwise, tumor assessments by the investigator will be used for the analysis.

5.1.1 Primary Endpoints

- Phase 1b part: Safety related endpoints including DLTs
- Phase 2 part: ORR is defined as the proportion of subjects who have best overall response (BOR) of CR or PR per RECIST 1.1

5.1.2 Secondary Endpoints

- BOR per RECIST 1.1 (for Phase 1b part)
- DOR is defined as the time from the first documentation of CR or PR to the first documentation of disease progression (PD) or death due to any cause (whichever occurs first), in subjects with confirmed CR or PR per RECIST 1.1
- DCR is defined as the proportion of subjects who have a BOR of confirmed CR or PR, or SD (after ≥5 weeks from the first dose) per RECIST 1.1
- CBR is defined as the proportion of subjects who have a BOR of confirmed CR or PR, or durable SD (duration of SD ≥23 weeks) per RECIST 1.1
- Safety and tolerability (eg, treatment-emergent adverse events [TEAEs], treatment-related adverse events) for E7386 in combination with pembrolizumab
- PK profile of E7386 when co-administered with pembrolizumab

5.1.3 Exploratory Endpoints

[redacted]

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

5.2.2 Subject Disposition

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

The number (percentage) of subjects who were treated, continued, or discontinued study drug at data cutoff date, along with the primary reason for discontinuation from the study drug will be presented. The number (percentage) of subjects who discontinued treatment but were on survival follow-up at data cutoff date will also be provided.

The number (percentage) of subjects who were on study or off study (ie, discontinued from the study) at data cutoff date and the primary reason for discontinuation from study will be presented.

5.2.3 Protocol Deviations

Important protocol deviation criteria will be established and subjects with important protocol deviations will be identified and documented before the database lock.

The number (percentage) of subjects with at least 1 important protocol deviation and the number (percentage) of subjects with each important protocol deviation, and all protocol deviations related to coronavirus disease 2019 (COVID-19) will be presented.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using the Efficacy Analysis Set for each dose level/tumor cohort, and for phase/overall (as needed) using descriptive statistics.

Continuous demographic and baseline variables include:

- Age
- Height
- Baseline weight (kg)
- Baseline body mass index (BMI) (kg/m^2)

Categorical demographic and baseline variables include:

- Age group:
  - <65 years
  - ≥65
- Sex
- Race
- Ethnicity
- Region/Country
- Eastern Cooperative Oncology Group - Performance Status (ECOG PS)
- New York Heart Association (NYHA) Classification

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In addition, previous anticancer medication, previous anticancer procedures and previous radiotherapy will be summarized.

The number (percentage) of subjects in the safety analysis set reporting a history of any medical condition, as recorded on the case report form (CRF), will be summarized.

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). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Efficacy Analysis Set for each dose level/tumor cohort, and for phase/overall (as needed) by Anatomical Therapeutic Chemical class 1, pharmacologic class 3, and WHO DD preferred term (PT). Prior medications are defined as medications that started before the first dose of study drug regardless if they were either stopped before the first dose of study drug or continued during the study. Concomitant medications are 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. Medications received after 30 days of last dose will be considered as post-treatment medications. The summary will be presented for each dose level/tumor cohort, and for phase/overall (as needed). A medication that cannot be determined as prior/concomitant/post treatment due to missing/incomplete dates will be regarded as a concomitant medication. All medications will be presented in subject data listings.

Any anticancer therapies (medication, procedure) received during survival follow-up and any palliative radiotherapy will also be summarized on the Efficacy Analysis Set.

5.2.6 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical research associates will review treatment compliance during site visits and at the completion of the study. Treatment compliance will not be summarized since the data will not be entered in the clinical database. Information on subject exposure to study drug is described in Section 5.6.1.

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

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5.3.5 Handling of Missing Data, Dropouts, and Outliers

No imputation will be performed for missing data.

5.4 Efficacy Analyses

All efficacy analyses (except for DOR) will be performed by dose level in the escalation part and within each cohort/tumor type for the expansion part on the Efficacy Analysis Set. The analysis for DOR will be performed in the subjects who show a confirmed CR or PR within each cohort/tumor type on the Efficacy Analysis Set.

BOR is CR, PR, SD, PD, or not evaluable (NE)/Unknown, where SD has to be achieved at ≥5 weeks after the first dose. If a subject had a BOR of non-CR/non-PD, the subject's BOR will be grouped with the SD category. The BOR of CR and PR requires confirmation by a subsequent assessment of response at least 28 days later.

5.4.1 Primary Efficacy Analyses

Phase 1b part:

There is no primary efficacy analysis, since the primary objective of Phase 1b part is to assess the safety and tolerability and determine the RP2D of E7386 in combination with pembrolizumab. Thus, the efficacy analyses for Phase 1b part are described in the subsequent sections according to the study endpoints.

Phase 2 part:

ORR is defined as the proportion of subjects achieving a BOR of CR or PR. All responses of CR and PR must be confirmed no less than 28 days following the initial achievement of the response. Estimated ORR and the corresponding Clopper-Pearson 2-sided 95% CI will be provided for each cohort/tumor type. A summary of BOR will also be presented.

5.4.2 Secondary Efficacy Analyses

BOR per RECIST 1.1 for Phase 1b part will be summarized in the same manner as described above.

Waterfall plots for maximum tumor shrinkage (ie, postbaseline nadir) in sum of diameters of target lesions will be provided.

DOR will be calculated for subjects whose BOR is confirmed CR or PR. It will be estimated and plotted over time using Kaplan-Meier method if necessary. Median and quartiles of DOR will be provided, alongside the 95% CIs. Range (minimum to maximum) of DOR will also be presented with the censored indicator '+' if applicable. The probability of DOR with its 95% CI at selected duration timepoints will be provided. The 95% CIs for the probability of DOR will be calculated. Censoring rules for DOR are the same as those of PFS (Table 2). Subjects who show a confirmed CR or PR and without disease progression or death will be censored at the time of the last tumor assessment. The summary of subjects with event/censor along with the reason for censor will also be provided.

DCR and CBR will also be calculated. Estimate of DCR and the corresponding Clopper-Pearson 2-sided 95% CI will be presented. CBR will be calculated for subjects whose BOR

is SD. Estimate of CBR and the corresponding Clopper-Pearson 2-sided 95% CI will be presented.

5.4.3 Other Efficacy Analyses

OS is defined as the time from the date of first dose to the date of death. All events of death will be included, regardless of whether the event happened while the subject was still taking study drug, or after the subject discontinued study drug. OS will be estimated and plotted over time using the Kaplan-Meier method. Median and quartiles will be provided, alongside 95% CIs. Range (minimum to maximum) of OS will also be presented with the censored indicator '+' if applicable. The probability of OS with its 95% CI at selected timepoints will be provided. Subjects who are lost to follow-up or withdrew consent will be censored at the last known alive date, or the data cutoff date, whichever occurs first. Subjects who remained alive will be censored at the data cutoff date. The summary of subjects with event/censor along with the reason for censor will also be provided.

PFS is defined as time from the date of first dose to the date of the first documentation of disease progression or death, whichever occurs first. PFS will be summarized in the same manner as OS. Subjects without PD or death will be censored at the time of the last tumor assessment. 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.

Censoring rules for PFS are given in Table 2 below.

Table 2 Censoring Rules for PFS

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or no postbaseline adequate tumor assessments[a]	Date of first dose	Censored
2	Death without disease progression or any new anticancer therapy	Date of death	Progressed
3	Progression documented between scheduled visits, on or prior to new anticancer therapy	Date of the first radiological PD assessment	Progressed
4	Death between adequate assessments (Death before next scheduled assessment or after exactly one missing assessment)	Date of death	Progressed
5	New anticancer treatment started	Date of last adequate radiological tumor assessment[a] prior to or on the date of new anticancer treatment	Censored
6	Death or progression after more than one consecutive missed tumor assessment[b]	Date of last adequate radiological tumor assessment[a] before missed tumor assessment	Censored
7	No progression	Date of last adequate radiological tumor assessment[a] prior to or on the date of data cut-off	Censored

CR = complete response, PD = progressive disease, PFS = progression-free survival, PR = partial response, SD = stable disease.

a. Adequate tumor assessment is radiological assessment of CR, PR, SD, non-CR/non-PD, or PD as determined by investigators at regular interval as defined in the protocol. Any tumor assessments after new anticancer treatment starts will be removed in the definition of PFS.

b. More than 1 consecutive missed tumor assessment is defined as if the duration between the last adequate radiological tumor assessment and PD or death is longer than 97 days [=((6+1) x 2 x 7)-1] for subjects on the every 6 weeks scanning schedule in this study; longer than (>) 139 days [= ((9+1) x 2 x 7) – 1)] for subjects on every 9 weeks tumor assessment schedule after CCI in this study

For subjects moving from one schedule to another:

Missed CCI and Week 33 assessments: (>)118 days [= ([(6+1) + (9+1)] x 7) – 1)]

The priority of the censoring rules is as follows:

If the subject had PD (No. 3) or death (No. 2, No. 4) prior to or on the date of data cut-off, the following sequence will be applied:

- If the No. 1 is applicable, the date of first dose will be used (censored). However, if the subject died (No. 2, No. 4) within 97 days (14 weeks -1 day) after the first dose and did not meet No. 5, the date of death will be the PFS event date (not censored).
- If the No. 5 before PD or death, and/or No. 6 are applicable, the earliest date of censoring will be used (censored).
- Otherwise, the earliest date of progression (No. 2, No. 3, No. 4) will be the PFS event date (not censored).

If the subject had neither PD (No. 3) nor death (No. 2, No. 4) prior to or on the date of data cut-off, the earliest date of censoring (No. 1, No. 5, No. 6, No. 7) will be used (censored), if the subject met multiple situations.

Censoring rules for OS are provided in Table 3 below.

Table 3 Censoring Rules for OS

No.	Situation	Date of Death or Censoring	Outcome
1	Death before or on data cut-off	Date of death	Death
2	Death after data cut-off	Date of data cut-off	Censored
3	Alive at data cut-off	Date of data cut-off	Censored
4	Lost to follow-up or withdrawal of consent before data cut-off	Date last known to be alive	Censored

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The PK analysis will be performed on the PK Analysis Set using plasma concentrations of E7386 in combination with pembrolizumab.

Phase 1b

Plasma concentrations of E7386 will be tabulated and summarized by part, dose level, day and time. Plasma concentrations will be summarized using descriptive statistics (number of subjects [n], mean, SD, minimum, median, maximum).

Mean (±SD) and individual plasma concentration vs. time profile plots will be produced for each E7386 dose on both linear and semi-log scales for CCI . The +SD bars will only be displayed on the linear-linear scale. Spaghetti plots of individual plasma concentration vs. time profile plots will be produced for each dose level, day and time using linear scales.

PK parameters will be derived by noncompartmental analysis according to User Manual 302-104.00-MNL for the Phase 1b part. PK parameters derived from plasma E7386 data from the Phase 1b cohort will include but will not be limited to:

C_{max}	Maximum drug concentration in plasma on Cycle 1 Day1 and Cycle 1 Day 8
t_{max}	Time to reach maximum (peak) drug concentration in plasma following drug administration on Cycle 1 Day 1 and Cycle 1 Day 8
$AUC_{(0-t)}$	Area under the concentration-time curve from zero time to time of last quantifiable concentration in plasma on Cycle 1 Day 1 and Cycle 1 Day 8
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Other PK parameters may be calculated as appropriate.

Phase 2

Plasma concentrations of E7386 will be tabulated and summarized by dose level, day and time. Plasma concentrations will be summarized using descriptive statistics (number of subjects [n], mean, SD, minimum, median, maximum).

Plasma concentration data for E7386 in the Phase 2 part will be used to conduct population PK analysis and/or graphical presentation by integrating plasma concentration data from the Phase 1b part and/or other studies. PK/PD relationships (ie, exposure-efficacy, exposure-safety, and exposure-biomarker relationships) will be modeled, if possible, using a mechanistic approach, for effects of study treatment. Exploratory/graphical analyses will be conducted for PK/PD evaluations, and, if possible, will be followed by model-based analyses for E7386. For population PK, PK/PD, and exposure-response analysis, the details will be described in a separately prepared analysis plan and its report, and the results will not be included in the CSR.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

PD, pharmacogenomics, and other biomarker analyses may be performed and reported separately. Details of these analyses will be described in a separate analysis plan.

5.6 Safety Analyses

DLTs will be evaluated by the dose level (if applicable) and total for Phase 1b part on the DLT Analysis Set.

The Safety Analysis Set will be used for all other safety analyses. Safety variables will be summarized on an "as treated" basis within each cohort/tumor type, and for phase/overall (as needed) using descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum for continuous variables; numbers and percentages for categorical variables).

Safety variables include TEAEs, clinical laboratory results, vital signs, CCI [redacted] ECOG PS. If needed, the changes from baseline will also be summarized. The summary will be presented by each cohort/tumor type, and by phase/overall as appropriate.

Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

The duration of treatment, total number of doses/infusions, total doses, dose intensity, and relative dose intensity will be summarized. These variables are defined per subject as follow:

- Duration of overall treatment (days) = Date of last dose of any study drug – Date of first dose of any study drug + 1
- Duration of E7386 (days) = Date of last dose of E7386 – Date of first dose of E7386 + 1
- Duration of pembrolizumab (days) = Date of last administration of pembrolizumab – Date of first administration of pembrolizumab + 1
- Duration of both drugs (days) = Date of one of the study drug is first discontinued – Date of first dose of both study drugs + 1
- Number of administrations of pembrolizumab = Total number of IV administrations
- Total doses (mg) of E7386 (mg) = Sum of all the actual doses of E7386
- Dose intensity (mg/day) of E7386 = Total doses / Duration of E7386
- Relative dose intensity (%) of E7386 = 100 × Dose intensity of E7386/ Planned starting dose for each cohort

The number (percentage) of subjects with dose interruption, dose reduction and treatment discontinuation due to adverse events (AEs) will be provided. To determine dose reductions and dose interruptions, the incorrect doses that were taken by mistake will not be taken into consideration. Dose reduction is only applicable to E7386, but not for pembrolizumab, as pembrolizumab dose is always 200 mg when it is administered.

Treatment interruptions are identified as zero doses which are preceded and followed by the same dose level.

- If the dose after the zero dose is lower than that before the zero dose, this dose change will be counted as a dose reduction, instead of a dose interruption.
- If the subject discontinued due to AEs from treatment permanently after the zero dose, it will be counted as a treatment discontinuation due to AEs, instead of a dose interruption.

For pembrolizumab, as long as a dose was administered for a cycle, then there is not an interruption for this cycle.

Subject data listings will be provided for all dosing records.

5.6.2 Adverse Events

5.6.2.1 Dose Limiting Toxicity

The number (percentage) of subjects with DLTs and reasons for DLTs will be summarized for DLT Analysis Set. Subject data listing will be provided for DLT records.

5.6.2.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) will also be captured in the database. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used to assess the severity of AEs.

A TEAE is defined as an AE that emerges during treatment (on or after the first dose date of study drug up to 30 days after the subject's last dose), having been absent at pretreatment (Baseline) or:

- Reemerges during treatment or up to 30 days following last dose of study drug, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment or up to 30 days following last dose of study drug relative to the pretreatment state, when the AE is continuous

The SAE is also counted as a TEAE if it emerges up to 90 days after the subject's last dose of study drug, or up to 30 days following cessation of study drug if the subject initiated new anticancer therapy, whichever is earlier.

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

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade.

An overview table, including the number (percentage) of subjects with TEAEs, TEAEs with CTCAE Grade 3 or above, treatment-emergent serious adverse events (SAEs), deaths, TEAEs leading to discontinuation from study drug, TEAEs leading to dose reduction, TEAEs leading to dose interruption, and TEAEs leading to dose reduction or interruption will be provided. Additionally, the TEAE by SOC and PT (any grade and grade ≥3, maximum grade 3, 4 and 5), TEAE by decreasing frequency of PT (any grade and grade ≥3, maximum grade 3, 4 and 5) will be summarized.

The number (percentage) of subjects with TEAEs leading to death, treatment-emergent serious adverse events (SAEs, fatal and non-fatal), TEAEs leading to discontinuation from study drug, TEAEs leading to dose reduction, TEAEs leading to dose interruption, and TEAEs leading to dose reduction or interruption will be summarized by MedDRA SOC and PT.

Similar summaries for treatment-related TEAEs will also be provided if deemed necessary. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment (any study drug).

Subject data listings of all AEs, all AEs leading to death, all SAEs, and all AEs with CTCAE Grade 3 or above will be provided.

Subject data listings of AEs leading to discontinuation from study drug, AEs leading to dose reduction, AEs leading to drug interruption, and all deaths will be provided for all treated subjects.

TREATMENT-EMERGENT ADVERSE EVENTS OF CLINICAL INTEREST

TEAEs of special interest for E7386 will be identified based on the review of safety data by Clinical and Pharmacovigilance. CCI [redacted]

TEAEs of special interest (AEOSI) for pembrolizumab will be summarized by the grouped terms and PT.

TREATMENT-EMERGENT ADVERSE EVENTS ASSOCIATED WITH COVID-19

COVID-19 related TEAEs will be summarized by PT and worst CTCAE grade. A subject data listing of COVID-19 related TEAE will be provided.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. 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. For all quantitative parameters listed in the protocol Section 9.5.1.4.5, the actual value and the change from Baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value, including off treatment assessment) will be summarized by visit using descriptive statistics. Qualitative parameters listed in the protocol Section 9.5.1.4.5 will be summarized using frequencies (number and percentage of subjects), and changes from Baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant postbaseline results.

Laboratory parameters will be categorized according to CTCAE, and shifts from baseline CTCAE grades to the worst postbaseline grades will be assessed.

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 results of LNH classification will be provided in a subject data listing.

The number (percentage) of subjects with postbaseline values worsened from Baseline (with at least 1 CTCAE grade increase) will be presented. Likewise, subjects with postbaseline values of CTCAE Grades 3 or 4 worsened from Baseline will also be summarized. When displaying the summary, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Laboratory tests such as [redacted] may be conducted in central laboratories in lieu of local labs for certain parameters due to site capability. In these situations, results from central lab may be combined with those from local lab for the same parameter in the analyses if applicable.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic blood pressure, pulse, respiratory rate, temperature, weight) and changes from Baseline will be presented by visit.

A subject data listing of vital signs will be provided.

5.6.5 Electrocardiograms

Descriptive statistics for ECG parameters including heart rate, PR interval, QT interval, QTc Bazett (QTcB) interval, QTc Fridericia (QTcF) interval, and RR interval, and changes from Baseline will be presented by visit.

Shift tables will present the worst postbaseline changes from Baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

A subject data listing of ECG will be provided.

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

Absolute QTcF interval prolongation:

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

Change from Baseline in QTcF interval:

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

5.6.6 Other Safety Analyses

Descriptive summary statistics for LVEF assessed on echocardiograms or MUGA scans and changes from baseline will be calculated. A subject data listing of LVEF will be provided.

Shift table for ECOG PS will present changes from baseline classification to worst postbaseline classification. A subject data listing of ECOG PS will be provided.

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5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled and labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the CSR.

5.9 Extension Phase Analyses

The Extension Phase data in disposition, exposure and key safety will be summarized in the same manner as described in Section 5 at the study closeout, if deemed appropriate. The results will be provided in a separate CSR addendum.

6 INTERIM ANALYSES

No formal interim analyses requiring database lock are planned. The interim futility data review using a snapshot of the database will be performed by the sponsor for each tumor cohort for consideration of potential cohort expansion in the Phase 2 doublet treatment cohorts. An interim futility data review will be conducted when the initial 15 subjects are enrolled in each tumor cohort and required tumor responses assessed by RECIST 1.1 by the investigator are met or sufficient follow-up are reached. Details of the interim futility data review is described in details in Section 9.7.3 of the study protocol.

7 CHANGES IN THE PLANNED ANALYSES

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8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 General Data Handling

Baseline

The baseline value is defined as the last non-missing value reported before first dosing.

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%

The following factors will convert days to months or years:

1 month = 30.4375 days

1 year = 365.25 days.

Time (years) from first diagnosis to first dose is:

(Date of first dose – Date of first diagnosis)/365.25.

Handling of Missing Data

No imputation will be performed for missing data.

Handling of Missing Dates

The following imputation algorithm will be used for partial or missing dates:

Date of Death (only for subjects that died)

- If only the day of the month is missing, the first of the month will be used to replace the missing day
- If both the day and the month are missing, "January 01" will be used to replace the missing information*
- If a date is completely missing, death date will be imputed as the last known alive date + 1 day

* The imputed death date will be compared with the last known alive date (date of censoring for survival). The maximum date (of the imputed death date, date of censoring for survival + 1) will be considered as the date of death.

Start Date of Subsequent Anticancer Therapy

- If only the day of the month is missing, the subsequent therapy will be assumed to start on the first of the month if this day is later than the last dosing date of study treatment. Otherwise, the subsequent therapy will be assumed to start on the next day of the last dosing date of study treatment

- If both the day and the month are missing, the subsequent therapy will be assumed to start on the "January 01" of the given year if this day is latter than the last dosing date of study treatment. Otherwise, the subsequent therapy will be assumed to start on the next day of the last dosing date of study treatment
- If a date is completely missing, it will be considered as missing

8.2 Efficacy Data Handling

Handling of missing data for tumor assessment result

For the calculation of ORR, DCR and CBR, subjects with missing response status (subjects who do not have adequate postbaseline tumor assessments result) will not be included in numerator, but included in denominator.

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

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

8.3 Safety Data Handling

Adverse Events

AEs with incomplete start dates will be considered treatment emergent if:

- Day and month are missing and the year is equal to or after the year of the first dose date
- Day is missing, and the year is after the year of the first dose
- Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date
- Year is missing, or
- Complete date is missing

Concomitant Medications

Medications will be considered concomitant if:

- Day and month are missing and the year is equal to or after the year of the first dose date
- Day is missing, and the year is after the year of the first dose
- Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date or
- Year is missing, or
- Complete date is missing

Visit and Analysis Windows

The visit recorded in CRF will be used for safety summary by visit. The purpose of visit windows for safety analyses is to provide a single record per subject per visit for the calculation of descriptive summary statistics for safety parameters (eg, laboratory values and vital signs, etc.), and change from baseline by visit, if a same visit has 2 or more observations. The observation closest to the target date will be used in by visit summaries. If 2 or more observations have the same distance to the target visit day, the one that has the highest CTCAE grade or is furthest away from the normal range and the earliest observation will be used.

Other safety analyses (eg, worst postbaseline grade in laboratory results) will include all observations within 30 days after the final dose of study treatment.

8.4 Pharmacokinetic Data Handling

PK parameters will be derived by noncompartmental analysis according to User Manual 302-104.00-MNL. Details on calculating population PK parameters and data handling will be described in a separate plan.

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

Statistical programming and analyses will be performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9.4 or higher, and/or other validated statistical software as required.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study tables, listings, and graphs (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

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

National Cancer Institute (NCI) Cancer therapy evaluation program Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, Nov 2017. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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