STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7766-G000-101
Study Protocol Title:	An Open-Label, Multicenter Phase 1/1b Study of Intratumorally Administered STING Agonist E7766 in Subjects with Advanced Solid Tumors or Lymphomas – INSTAL-101
Date:	22 August 2022
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ATC	anatomical therapeutic class
AUC	area under the concentration-time curve
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	maximum observed concentration
CR	complete response
CRC	colorectal cancer
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	dose de-escalation
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
E	dose escalation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EI	equivalence interval
HNSCC	head and neck squamous cell carcinoma
iCPD	confirmed progressive disease per iRECIST
iCR	complete response per iRECIST
IIR	independent imaging review
iRECIST	modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics
iSD	stable disease per iRECIST
iUPD	unconfirmed progressive disease per iRECIST

Abbreviation	Term
LDi	longest axis diameter of a lesion
LLT	lower level term
LVEF	left ventricular ejection fraction
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI-2	improved modified toxicity probability interval
MUGA	multigated acquisition
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAVA	pooled adjacent violators algorithm
PD	pharmacodynamic, progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
Q1	25^{th} percentile
Q3	75^{th} percentile
Q3W	once in 3 weeks
QTc	corrected QTc interval
QTcF	corrected for QTc interval using Frederica's correction factors
R	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
S	staying at the current dose
SAP	statistical analysis plan
SD	standard deviation or stable disease

Abbreviation	Term
SDi	shortest axis perpendicular to the LDi
STING	stimulator of interferon genes
SOC	system organ class
TL	target lesion
t_{max}	time at which the highest drug concentration occurs
$t_{½}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
TLGs	tables, listings, and graphs
TNM	tumor-node-metastasis
Vd/F	apparent volume of distribution
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Study E7766-G000-101.

3.1 Study Objectives

3.1.1 Primary Objectives

The primary objectives of the study are:

Dose Escalation Part

- Assess the safety/tolerability profile of E7766 administered intratumorally in subjects with advanced solid tumors or lymphomas
- Determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of E7766 in subjects with advanced solid tumors or lymphomas

Dose Expansion Part

- Assess the safety/tolerability profile of E7766 administered intratumorally in cohorts of subjects with selected tumor types
- Assess clinical activity of E7766 based on investigator assessment of objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) according to modified Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and modified RECIST 1.1 for immune-based therapeutics (iRECIST) for solid tumors, in cohorts of subjects with selected tumor types

3.1.2 Secondary Objectives

The secondary objectives of the study are:

Dose Escalation part

- Evaluate preliminary clinical activity of E7766 based on investigator assessment of ORR, DOR, and DCR according to modified RECIST 1.1 and iRECIST for solid tumors
- Evaluate the pharmacokinetic (PK) profile of E7766 and any metabolites in plasma, urine, and feces

Dose Escalation and Dose Expansion parts

- Evaluate the PK profile of E7766 and any metabolites in plasma

- Evaluate progression-free survival (PFS) based on investigator assessment and overall survival (OS) in subjects treated with E7766
- Evaluate tumor size changes per investigator assessment in injected lesions

3.1.3 Exploratory Objectives

The exploratory objectives of the study are:

Dose Escalation and Dose Expansion Parts

- Evaluate changes in tumor size assessed by independent imaging review (IIR) using volumetric computed tomography (CT)/magnetic resonance imaging (MRI)
- Evaluate immune pharmacodynamics effects of E7766 in the tumors and in peripheral blood
- Explore PK/pharmacodynamics relationships (safety and efficacy endpoints)
- Explore correlation of baseline tumor and peripheral blood immune phenotypes and of STING genotypes with safety and/or efficacy endpoints
- Evaluate pre-injection changes in size of injected lesion per investigator assessment in addition to the scheduled tumor assessments to characterize the kinetics of response, progression, or immune-induced flare in the injected lesion

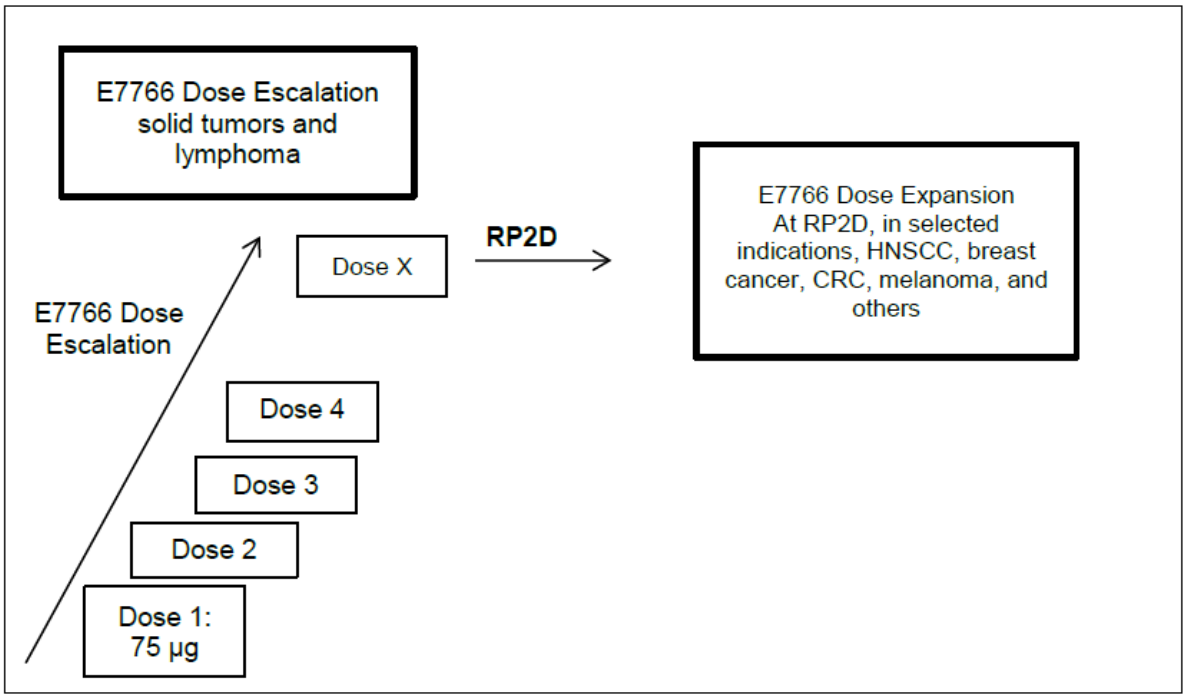
3.2 Overall Study Design and Plan

This is an open label, multicenter, Phase 1/1b study to assess the safety and evaluate the clinical activity of E7766 administered intratumorally to subjects with advanced solid tumors or lymphomas. A Dose Escalation part will enable selection of a dose of E7766 to move forward with as the RP2D in the Dose Expansion part, where clinical activity in selected tumor types or populations will also be evaluated.

Dose escalation will be conducted using an improved modified toxicity probability interval (i.e. mTPI-2) design (Guo et al., 2017; Yan et al., 2017) to determine the MTD for E7766. Each subject will be assessed for tumor response (injected and noninjected lesions), PK, and pharmacodynamics (blood and tumor factors). The RP2D will be selected based on integrating results of safety (including the MTD), clinical activity, PK, and pharmacodynamics. During the Dose Escalation part, selected dose level cohorts may accrue additional subjects to provide further safety, drug administration-related, biomarker, and/or PK data needed for selection of the RP2D. Intrapatient dose escalation of study drug will be allowed in the study.

The Dose Expansion part will be initiated when the RP2D and/or MTD is available from the Dose Escalation part. In the Dose Expansion part, separate study arms will evaluate E7766 at the RP2D in selected tumor types and populations to confirm safety and assess clinical activity. The study populations will be decided based on the emerging data from the Dose Escalation part.

The overall study design is shown in Figure 1.



CRC = colorectal cancer, HNSCC = head and neck squamous cell carcinoma, RP2D = recommended Phase 2 dose.

Figure 1 Study Schematic for Dose Escalation and Dose Expansion Parts

A fixed E7766 dose will be administered for each subject. There will be no adjustments for subject weight.

E7766 will be administered in cycles which are 3-weeks long, with treatment as follows:

- Induction (Cycle 1): injection on Days 1, 8, and 15
- Maintenance (Cycle 2 and after): injection on Day 1 of each cycle, once in 3 weeks (Q3W)

Approximately 35 to 40 subjects will be enrolled in the Dose Escalation part and 80 subjects will be enrolled in the Dose Expansion part.

The end of the study will be the date of data cutoff for the final analysis or last subject/last visit, whichever occurs later.

3.2.1 Dose Escalation

3.2.1.1 Dose Escalation Design

Dose assignment of subjects will be done using the improved mTPI (i.e mTPI-2) design in order to determine the MTD of E7766. Each subject will be assigned a dose in accordance with the rules of the mTPI-2 design based on a target dose-limiting toxicity (DLT) rate of 25% and its equivalence interval (EI) of 20% to 30%.

The dose assignment decision rule is pre-tabulated in the Decision Rule for Dose Assignment (Table 1). Dose assignment for the next dose will be determined according to the Method for Deciding the Dose of the Next Dose Group (Table 2) after consultation between the investigators and the sponsor. Subjects who are not evaluable for DLT should be replaced within their dose level, if at least 2 subjects in total have not been tested at the dose level. Subject enrollment will be closed when the DLT rate at the lowest dose level greatly exceeds the target DLT rate (25%) or when the RP2D has been determined.

Additional details of the mTPI-2 design are presented in Section 5.3.6.

Table 1 Decision Rule for Dose Assignment

Number of Patients with DLTs	Number of Patients																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU *	D	D	D	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E
3			DU	DU	DU	D	D	D	D	D	S	S	S	S	S	E	E	E	E	E
4				DU	DU	DU	DU	DU	D	D	D	D	D	S	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D
7							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12												DU	DU	DU	DU	DU	DU	DU	DU	DU
13													DU	DU	DU	DU	DU	DU	DU	DU
14														DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU

	Number of Patients																			
16																**DU**	**DU**	**DU**	**DU**	**DU**
17																	**DU**	**DU**	**DU**	**DU**
18																		**DU**	**DU**	**DU**
19																			**DU**	**DU**
20																				**DU**

Target DLT rate at MTD = 25% and its equivalence interval = 20% to 30%.
Display for more than 20 subjects at the current dose is omitted. If the required rules are not available in the table, the decision will follow the rule determined by the improved mTPI (i.e. mTPI-2) design with the same settings above.
Decision Table was calculated via East Bayes (EB 1.0.0).
D = De-escalate to the next lower dose, DLT = dose-limiting toxicity, E = Escalate to the next higher dose, MTD = maximum tolerated dose, mTPI = modified toxicity probability interval, S = Stay at the current dose, U = Current dose is unacceptably toxic (ie, Do not re-enter the current dose).
a: Extra subjects may be added for the lowest dose, for example if the investigators and the sponsor determine that more subjects would be required to adequately evaluate that dose level and it is considered safe to do so.

Table 2 Method for Deciding the Dose of the Next Dose Group

Dose Escalation Steps	E7766-Related Toxicity During Cycle 1
Increase ~75% to 100%	Up to Grade 1
Increase ~30% to 60%	Grade 2 in 1 subject
Increase ~10% to 30%	Grade 2 in 2 or more subjects and/or Grade 3 or higher in 1 or more subject

3.2.1.2 Dose-Limiting Toxicities

A subject should have received at least 2 E7766 injections during the DLT period (Cycle 1) to be considered evaluable for a DLT, unless the subject experienced a treatment-related toxicity preventing more than 1 administration of E7766.

If a subject at a given dose level receives fewer than 2 out of the 3 planned E7766 intratumoral injections during the Induction cycle (ie, the DLT period/Cycle 1) because of E7766-related adverse events (AE), the subject should be considered as potentially experiencing a DLT by the Study Safety Committee, composed of investigators and representatives of the sponsor.

3.2.1.3 Selection of RP2D

The RP2D of E7766 will be selected based on an integrated evaluation of safety, tolerability, clinical activity, PK data, and any available pharmacodynamics data for all dose levels or all available data.

The investigators and sponsors will together conduct the evaluation and the recommended Phase 2 dose/doses and/or any modification to the dosing regimen will be agreed upon jointly.

3.2.2 Dose Expansion

Expansion arms shall be opened in specific tumor types and populations with treatment at the E7766 RP2D.

Safety and clinical activity of E7766 at the RP2D will be tested in separate expansion arms with defined populations potentially including but not limited to melanoma, HNSCC, breast cancer, colorectal cancer, and/or other tumors. About 40 patients will be recruited in each expansion arm.

Note that according to the corporate decision made on April 26, 2022, no subjects will be enrolled for dose expansion part. There will be no analysis for dose expansion part.

4 DETERMINATION OF SAMPLE SIZE

It is anticipated that selection of the RP2D will be based on integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamics data. The total number of subjects for the Dose Escalation part will depend on the observed data including safety profile, which will determine the number of subjects per dose level, as well as the number of dose levels tested before the RP2D is established. Therefore, a formal statistical calculation of sample size is not applicable. The anticipated sample size for E7766 in the Dose Escalation part will be approximately 35 subjects, assuming approximately 10 dose levels and at least 2 subjects per dose level will be tested to achieve the MTD and then approximately 4 subjects for the selected 1 to 3 dose levels may be additionally enrolled for the RP2D selection.

The total number of subjects for the Dose Expansion part will depend on the number of arms by the disease-specific indications, and the number of subjects per arm. The anticipated sample size for the Dose Expansion part will be approximately 80 subjects, assuming 2 arms, and a maximum of 40 subjects per arm will be enrolled.

5 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the data cutoff for the abbreviated Clinical Study Report (CSR) or the study is completed and the database is locked and released. Statistical analyses will be performed using SAS® software or other validated statistical software as required.

The data cutoff for the abbreviated CSR will be done after 6 months after the last subject in (i.e. last subject started treatment), and may be conducted before the last subject discontinues study treatment in this study.

In general, continuous variables will be summarized using descriptive statistics such as mean, standard deviation (SD), median, 25th percentile (Q1), 75th percentile (Q3), minimum,

and maximum. Categorical variables will be summarized using frequency and percentage. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries.

Summary will be presented by initial dose level/arm and total for each part, and overall. Details will be provided in a separate Table Figure Listing document.

5.1 Study Endpoints

5.1.1 Primary Endpoints

- Safety-related endpoints, including DLT
- ORR according to modified RECIST 1.1 and iRECIST, defined as the proportion of subjects achieving a best overall response (BOR, see Appendix **Error! Reference source not found.**) of confirmed partial response (PR) or complete response (CR). Subjects who do not have a tumor response assessment for any reason will be considered nonresponders and will be included in the denominator when calculating the response rate (Dose Expansion part only)
- DOR according to modified RECIST 1.1 and iRECIST, defined as the time from the date of first documented and confirmed PR or CR until the first documentation of qualified disease progression (see Section 5.4.2.4) or death, whichever occurs first (Dose Expansion part only)
- DCR according to modified RECIST 1.1 and iRECIST defined as the proportion of subjects achieving BOR as PR or CR or stable disease (SD) (Dose Expansion part only)

5.1.2 Secondary Endpoints

- ORR, DOR, and DCR according to iRECIST and modified RECIST 1.1 (Dose Escalation part only)
- PK profile in plasma, urine, and feces (Dose Escalation part) and plasma only (in Dose Expansion part)
- PFS, defined as the time from the date of first dose to the date of the first documentation of qualified disease progression (see Section 5.4.2.4) or death, whichever occurs first
- OS, defined as the time from the date of first dose to the date of death from any cause
- Change in tumor size in injected lesions

5.1.3 Exploratory Endpoints

- Changes in tumor size assessed by IIR using volumetric CT/MRI

- Immune pharmacodynamics effects of E7766 in the tumors and in the peripheral blood
- PK/pharmacodynamics relationships (safety and efficacy endpoints)
- Baseline immune phenotypes and its relationship with the response to E7766
- STING genotypes and its relationship with the response to E7766
- Changes in pre-injection size of injected lesion per investigator assessment

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

DLT Analysis Set is the group of subjects in the Dose Escalation part who have completed Cycle 1, without incurring certain major protocol deviations (for instance those related to dosing or others identified before database lock), with at least 2 E7766 injections during Cycle 1, and are evaluable for DLT, or subjects who have experienced DLT during Cycle 1. This will be the analysis set to evaluate tolerability.

Full Analysis Set is the group of subjects who received at least 1 dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics.

Safety Analysis Set is the same group as Full Analysis Set. This will be the analysis set for all safety evaluations except DLT results.

Efficacy Analysis Set is the group of subjects who received at least 1 dose of study drug and had a baseline tumor assessment. This will be used for supportive analysis of ORR.

Pharmacodynamic Analysis Set and Pharmacokinetic/Pharmacodynamic Analysis Set are defined in separate PK or PK/PD analysis plan(s).

5.2.2 Subject Disposition

The number (percentage) of enrolled (i.e., signed informed consent) and treated subjects will be summarized as well as subjects who completed the study or discontinued from the study, with reasons for discontinuation.

The number (percentage) of subjects who completed the study treatment/discontinued from the study treatment and reasons for discontinuation will also be summarized.

Subject data listings for the disposition of screening, treatment, and study will be provided.

5.2.3 Protocol Deviations

All major protocol deviations will be determined and documented based on the review of individual subject data prior to database lock.

Major protocol deviations will be listed and summarized on Full Analysis Set.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Full Analysis Set will be summarized using descriptive statistics.

Continuous demographic and baseline variables including age, weight, height and time since first diagnosis (months) will be summarized and presented as N, mean, standard deviation, median, Q1, Q3, minimum and maximum values.

For categorical variables such as sex, age group (e.g., <65, >=65), race, ethnicity, geographic region, Eastern Cooperative Oncology Group (ECOG) performance status, New York Heart Association (NYHA) cardiac disease classification, type of tumor diagnosis, location of primary tumor, histology/cytology of the primary tumor, and tumor staging (tumor-node-metastasis [TNM] classification), the number and percentage of subjects will be presented.

Previous therapies (anticancer medication, procedure, and radiotherapy) will also be listed and summarized.

Medical History

The history of any medical condition, as recorded on the case report form (CRF), will be listed.

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) Version of March 2019 or later.

The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Full Analysis Set by Anatomical Therapeutic Chemical (ATC) class (ie, Anatomical class, Pharmacological class) and WHO DD preferred term. Prior medications will be defined as medications that started before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 90 days after the subject's last dose. Note that a medication can be classified as both prior and concomitant, if the medication started before the first dose of study drug and continued after the first dose.

All medications will be presented in subject data listings.

Anticancer therapies (medication, procedure) received during survival follow-up will also be listed.

5.2.6 Treatment Compliance

Treatment compliance related major protocol deviations will be presented as provided in Section 5.2.3. 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 comparisons will be performed for this study.

5.3.4 Examination of Subgroups

Subgroup analyses may be conducted, if deemed appropriate.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

Treatment Related TEAEs include TEAEs that were considered by the Investigator to be related to study drug or TEAEs with a missing causality.

Medications will be considered concomitant if:
a) Day and month are missing and the year is equal to or after the year of the first dose date;
b) Day is missing, and the year is after the year of the first dose;
c) Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date; or
d) Year is missing; or
e) Complete date is missing.

For efficacy endpoints, missing assessments will not be imputed. For incomplete dates involving efficacy and safety data such as adverse events, concomitant medications, laboratory assessments, vital signs, and echocardiogram/multigated acquisition (MUGA) data, a conservative imputation will be used for calculation if needed. The imputation rules will be specified in study analysis dataset specification with more details.

5.3.6 Other Considerations

Improved Modified Toxicity Probability Interval Design (mTPI-2) in Dose Escalation Part

The mTPI-2 design, which uses a Bayesian statistical framework and a beta-binomial hierarchical model, will be employed to determine the MTD and/or RP2D of E7766.

Decision rules for dose assignment will be based on the mTPI-2 design with the target DLT rate of 25% and its equivalence interval (EI) of 20% to 30%, and a set of equal-width intervals as EI below/above EI (ie, below EI: 0% to 10%, 10% to 20%; above EI: 30% to 40%, ... , 90% to 100%). The posterior probabilities of each interval will be calculated with non-informative beta prior distribution Beta (1, 1). The location of the interval with the largest posterior probability—below EI, EI, or above EI—guides the decision for the next dose level to be assigned, ie, Dose Escalation (E), Staying at the current dose (S), or dose De-escalation (D), respectively. This dose assignment rule minimizes the posterior expected penalty in the Bayes' rule under a decision-theoretic framework with the equal prior expected penalties for E, S, and D. The entire dose assignment decision rule can be pre-tabulated as presented in Table 1.

The subject enrollment will be closed when the lowest dose has a >95% posterior probability of being above the target DLT rate of 25% (ie, an unacceptable DLT rate beyond the target DLT rate) or when the RP2D has been determined.

The MTD is defined as the dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate at each dose among all the tested doses with a ≤95% posterior probability of being above the target DLT rate of 25%. The isotonically transformed posterior mean under the beta posterior distribution with non-informative beta prior distribution Beta (0.005, 0.005) will be used to determine the estimate of DLT rates at each dose. The pooled adjacent violators algorithm (PAVA; Bartholomew et al., 1983) will be used to maintain monotonically the increase of DLT rate with increasing dose level. Late immune-related toxicities occurring after Cycle 1 (DLT period) and up to 90 days after last dose of E7766, will also be used to inform corrections to the MTD and aid selection of the RP2D.

5.4 Efficacy Analyses

All efficacy analyses will be primarily performed on the Full Analysis Set. As supportive analysis, summary of ORR will also be performed on the Efficacy Analysis Set.

5.4.1 Primary Efficacy Analyses

5.4.1.1 Dose Escalation Part

There will be no primary efficacy analysis since the primary objective of the Dose Escalation part is to assess the safety/tolerability and to determine the MTD and/or RP2D. Thus, the efficacy analyses are described in the subsequent sections according to the study endpoints.

5.4.1.2 Dose Expansion Part

Objective Response Rate

ORR will be calculated with exact 95% confidence interval (CI) using Clopper and Pearson method. Summary of best overall response will be provided.

For subjects with solid tumors, swimmer plots based on modified RECIST 1.1 may also be presented as appropriate.

Duration of Response

DOR will be summarized using Kaplan-Meier estimates as appropriate. Median, Q1, Q3, and their 95% CIs estimated using generalized Brookmeyer and Crowley method will be presented. Kaplan-Meier estimates of DOR will be plotted over time. The DOR will be based on subjects achieving a best overall response of confirmed PR or CR.

Disease Control Rate

DCR will be calculated with exact 95% CI using Clopper and Pearson method.

5.4.2 Secondary Efficacy Analyses

5.4.2.1 Objective Response Rate for Dose Escalation Part

ORR for Dose Escalation part will be evaluated in the same manner as described in Section 5.4.1.2 for Dose Expansion part.

5.4.2.2 Duration of Response for Dose Escalation Part

DOR for Dose Escalation part will be evaluated in the same manner as described in Section 5.4.1.2 for Dose Expansion part.

5.4.2.3 Disease Control Rate for Dose Escalation Part

DCR for Dose Escalation part will be evaluated in the same manner as described in Section 5.4.1.2 for Dose Expansion part.

5.4.2.4 Progression-free Survival

In PFS analysis Subjects without disease progression or death will be censored at the time of the last tumor assessment. Subjects who started new anticancer therapies without documented progression of disease will be censored at the last adequate tumor assessment on or prior to the start of new anticancer therapies. Determination of the date of PFS event or censoring is summarized in Table 3 below.

Table 3 PFS Event and Censoring Rules

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or postbaseline adequate tumor assessments	Date of first dose	Censored
2	Progression documented between scheduled visits, on or prior to new anticancer therapy	Date of first qualified*** PD assessment	PFS Event
3	No progression at the time of data cutoff	Date of last adequate assessment on or prior to data cutoff	Censored
4	New anticancer therapy started	Date of last adequate assessment on or prior to the start of new anticancer therapy	Censored
5	Death before first PD assessment, on or prior to start of new anticancer therapy	Date of death	PFS Event
6	Death between adequate assessment*	Date of death	PFS Event
7	Death or progression after more than one missed visit/tumor assessment**	Date of last adequate assessment before missed tumor assessments	Censored

CR = complete response, ic = iRECIST-confirmed, iu = iRECIST-unconfirmed, PD = progressive disease, PR = partial response, SD = stable disease.

Note:

* Adequate tumor assessment is radiologic 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 therapy will not be considered in the definition of PFS.

** More than one missed visit/adequate tumor assessment is defined as:

- having the duration between two consecutive tumor assessments or the duration between the last adequate tumor assessment and death/PD being longer than (>) 97 days (for solid tumors because the scans are scheduled every 6 weeks ±7 days for this study).

*** Qualified PD is defined as:

- For modified RECIST: the documented PD per modified RECIST CRF page;
- For iRECIST: in the order of 1) the documented iCPD per iRECIST CRF page, or 2) the iUPD that has not be reset by subsequent iCR/iPR/iSD

NOTE: iCPD has to be within 8 weeks of iUPD, but not earlier than 4 weeks (i.e. >=28 days) of iUPD.

1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have baseline or postbaseline adequate tumor assessments (No. 1), the subject will be censored at the date of the first dose. However, if the subject died within 35 days after the first dose date and did not receive any new anticancer therapy, it will be counted as a PFS event at the date of death.
- If subject has baseline tumor assessment but does not have any postbaseline adequate tumor assessments, the subject will be censored at the date of the first dose. However, if the subject died

within 97 days after the first dose date and did not receive any new anticancer therapy, it will be counted as a PFS event at the date of death.

- If a subject has a baseline and at least one post-baseline adequate tumor assessment and had new anticancer therapy before PD or death (No. 4), the subject will be censored at the date of the last adequate tumor assessment on or prior to the date of new anticancer therapy
- If a subject missed two or more tumor assessments (No. 7), the subject will be censored at the date of the last adequate tumor assessment before the occurrence of more than one missing assessment. Note that if a subject is censored by both of this criterion and start of new anticancer therapy criterion, the earliest censoring date will be used.
- Otherwise, if a subject had PFS 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).

PFS will be presented in subject data listings.

5.4.2.5 Overall Survival

OS is defined as the time from the date of first dose to the date of death from any cause.

Subjects who are lost to follow up or withdrew consent will be censored at the date subject was last known to be alive, or the cutoff date, whichever occurs first. Subjects who remained alive will be censored at the time of data cutoff. Determination of the date of OS event or censoring is summarized in Table 4 below.

Table 4 OS Event and Censoring Rules

Situation	Date of Event or Censoring	Outcome
Death no later than data cut-off date	Date of death	OS Event
Death after data cut-off	Date of data cut-off	Censored
Subject still alive at data cut-off	Date of data cut-off	Censored
Subject lost to follow-up or withdrawal of consent before data cut-off	Date of last known to be alive	Censored
Note: date of subject disposition may be used as last known alive date if the disposition reason is Subject Choice, Withdrawal consent and Treatment ongoing at data cut-off.		

OS will be presented in subject data listings.

5.4.2.6 Change in Tumor Size in Injected Lesions

For subjects with solid tumors based on modified RECIST 1.1 and iRECIST (if appropriate) assessments, a waterfall plot will be presented for the maximum percent change from baseline

in injected lesions. If a subject has multiple lesions injected, the first injected lesion will be included.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

Plasma concentrations of E7766 will be tabulated and summarized by dose level, day, and protocol specified time. Urine and fecal recovery of E7766 will be tabulated and summarized by dose level, day, and protocol specified collection interval.

The Safety Analysis Set will be used for individual plasma concentration listings. The Pharmacokinetic Analysis Set will be used for all other analyses such as the summaries of plasma concentrations.

E7766 PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated:

- C_{max} - Maximum drug concentration;
- t_{max} - Time to reach Cmax following drug administration;
- AUC - Area under the concentration-time curve;
- t½ - apparent terminal half-life (if data permit);
- CL/F - Apparent total body clearance;
- Vd/F - Apparent volume of distribution;
- R - Accumulation ratio post multiple doses;
- fe - fraction of administered drug excreted/recovered in urine and feces.

Details of the PK analyses will be described in a separate analysis plan and the results will be presented in a separate report. Metabolite PK will also be summarized in this report if exploratory characterization/identification of metabolites in urine and plasma is attempted depending on emerging nonclinical data.

Any exploratory population PK or PK/PD modeling and simulation work, if done, will be described in details in a separate plan and a separate report.

These plans and reports, if done, will be referenced and the high-level results and conclusions will be summarized in the clinical study report.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The effect of E7766 treatment on blood and/or tissue biomarkers, and/or immune cell subsets will be summarized using descriptive statistics. Pharmacodynamic, pharmacogenomic, and other biomarker analyses will be performed and reported separately.

Details of these analyses will be described in a separate analysis plan and reported separately.

5.6 Safety/Tolerability Analyses

Evaluation of DLTs will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated.

All safety analyses will be performed on the Safety Analysis Set. Safety data will be summarized on an "as treated" basis using descriptive statistics.

Safety variables include treatment-emergent AEs (TEAEs), clinical laboratory parameters, vital signs, 12-lead electrocardiogram (ECG), ECOG performance status, echocardiogram/MUGA results including left ventricular ejection fraction (LVEF).

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, number of study drug administered, and number of subjects requiring dose reductions and dose omission will be summarized.

5.6.1.1 Extent of Exposure to Study Drug

The total number of treatment cycles for each subject is the largest cycle number in which a subject receives any non-zero dose of study drug.

The treatment duration (days) will be calculated as the minimum of (day 1 of the last cycle with non-zero dose+21 days, or treatment disposition date) – date of the first non-zero dose.

5.6.1.2 Study Drug Administered

The total number of dose administrations and total cumulative dose (μg) received per subject, and relative dose intensity will be summarized with descriptive statistics.

The total number of doses received per subject will be calculated as the total number of injections with non-zero doses administered during the study per subject. The total cumulative dose per subject (μg) will be calculated as the sum of all doses (μg) that subject has actually received during the study. The relative dose intensity, which is defined as the ratio (%) of total

dose received and total planned dose (i.e., received dose as a percentage of sum of planned doses), will be calculated.

Number of injected lesions per subject will also be summarized.

5.6.1.3 Study Drug Dose Modifications

The guidance of E7766 dose modifications for Dose Escalation part and Dose Expansion part are outlined in protocol.

Dose reduction refers to a situation that a planned dose level was reduced from the previous dose level without going back the previous dose level. Dose omission only refers to the scenario that the dose levels before and after omission period (defined as the period with planned dose=0) are the same. If the subject discontinued from treatment permanently after dose omission with planned dose=0, it should be counted as treatment discontinuation instead of dose omission.

The number of subjects with dose reductions and dose omission will be summarized.

Subject data listings will be provided for all dosing records.

5.6.2 Adverse Events

5.6.2.1 Dose Limiting Toxicity

The number and percentage of subjects with DLT 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). Adverse events will be coded to the MedDRA (Version 21.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that emerges during treatment (on or after the first dose of study drug up to 90 days after the subject's last dose) or start day of another anticancer therapy, whichever is earlier; or in case subject has initiated new anticancer therapy within 30 days, the AEs occurring for 30 days following the last dose of study drug, having been absent at pretreatment (baseline) or

- Reemerges during treatment, having been present at pretreatment (baseline) but stopped before treatment, or

- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous, or

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.

Overview of TEAEs

An overview of TEAEs reported through the study will be provided. Overall summary of TEAE will include the number and percentage of subjects with TEAEs, serious TEAEs, TEAEs of Grade 3 or higher, TEAEs leading to treatment discontinuation, TEAEs leading to dose reductions, TEAEs leading to dose interruptions, and TEAEs with fatal outcomes. Similar summaries for treatment-related TEAEs will also be provided.

All TEAEs

All TEAEs will be summarized 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 TEAEs will also be summarized by SOC, PT, and worst Common Terminology Criteria for Adverse Events (CTCAE) grade.

Treatment-related TEAEs

Treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. Treatment-related TEAEs will also be summarized by SOC, PT, and worst CTCAE grade.

Grade 3 or higher TEAEs

The grade 3 or higher TEAEs will be summarized by SOC and PT. A subject data listing of grade 3 or higher AEs will be provided.

Serious TEAEs

Serious TEAEs will be summarized by SOC and PT. Similar summary for treatment-related serious TEAEs may also be presented. A subject data listing of all SAEs will be provided.

TEAEs Leading to Treatment Discontinuation

The TEAEs leading to discontinuation from study drug will be summarized by SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

TEAEs Leading to Dose Reductions and Dose Interruptions

The TEAEs leading to dose reductions and/or dose interruptions will be summarized by SOC and PT. A subject data listing of AEs leading to dose reductions and/or dose interruptions of study drug will be provided.

TEAEs with Fatal Outcome

The TEAEs with fatal outcome will be summarized by SOC and PT. Similar summary for treatment-related TEAEs with fatal outcome may also be presented.

A subject data listing of AEs with fatal outcome will be provided. A listing of the AEs with fatal outcome not due to PD may also be provided.

Deaths

The number of subjects who died during the study will be summarized. In addition, the number of deaths within 90 days of last dose will also be presented.

A listing of subjects who died during the study will be provided.

5.6.3 Laboratory Values

Clinical laboratory tests to be performed for this study, including hematology, chemistry, and urinalysis.

Laboratory results will be summarized using standard units, as appropriate.

Laboratory parameters will be graded according to CTCAE Version 5.0. In the summary of laboratory parameters by CTCAE grade, for parameters with CTCAE grading in both high and low direction (eg, calcium, glucose, magnesium, potassium, sodium), CTCAE grades in both high and low directions will be summarized separately.

Descriptive statistics for values and changes from baseline at each scheduled visit for quantitative hematology and chemistry laboratory parameters will be provided. Boxplots of laboratory values over time may be provided for selected hematology and chemistry parameters for subjects in the expansion cohort.

In selected hematology and chemistry parameters, the worst CTCAE grade postbaseline and shift from baseline will be summarized in shift tables. Subject with nonmissing baseline and postbaseline results will be used as denominators in shift tables.

Calcium corrected for albumin (mmol/L) will be calculated as:

Calcium measured (mmol/L) + 0.025 (40 - Albumin (g/L)).

if result for Albumin is > 40 g/L, then calcium corrected for albumin (mmol/L) = Calcium measured (mmol/L).
if albumin was missing, then calcium corrected for albumin is missing

5.6.4 Vital Signs

Descriptive statistics for vital sign 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

ECG data includes 24 hour continuous Holter ECG, central and local 12-lead ECG data.

Only local ECG data will be used for safety analysis. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit. Shift tables will be presented for the changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to worst postbaseline category.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia (QTcF) postbaseline 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

A subject data listing of local ECG only will also be provided.

5.6.6 Other Safety Analyses

5.6.6.1 Left Ventricular Ejection Fraction

LVEF assessed on echocardiogram or MUGA scans will be listed.

5.6.6.2 Eastern Cooperative Oncology Group Performance Status

Shift table for ECOG performance status will be presented for the change from baseline classification to the worst postbaseline classification.

A subject data listing of ECOG performance status will be provided.

5.7 Other Analyses

No other analysis is planned.

5.8 Exploratory Analyses

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

6 INTERIM ANALYSES

No formal interim analysis is planned for this study.

Interim monitoring using a snapshot of the database will be conducted to determine the MTD and/or RP2D, or to confirm safety and detect efficacy signals in subjects with selected disease indications before the analysis for CSR. Database locks are not required to perform these interim evaluations.

7 CHANGES IN THE PLANNED ANALYSES

MTD is not determined due to early termination of dose escalation part. As no subjects will be enrolled for dose expansion part, analysis for expansion arm will not be conducted.

There will be an abbreviated CSR, the following analysis planned will be removed:

- Protocol deviations
- Medial history and Prior and concomitant medications
- ECOG
- Listings for tumor assessment
- Efficacy analysis for efficacy analysis set
- MUGA or Echocardiogram

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Visit Windows

The purpose of this windowing is to provide a single record per subject per visit for the calculation of descriptive statistics per scheduled visit, and change from baseline per visit. In the calculation of by-visit analysis for laboratory values and vital signs, if multiple observations occurred on the same visit, the scheduled record will be used for summary tables. Other safety analyses (e.g., worst grade laboratory results and shift tables) will include all postbaseline assessments, including those scheduled and unscheduled visits.

8.2 Baseline Definitions

In general, baseline value is defined as the last non-missing measurement taken on or prior to the first dose date. In particular, for laboratory assessments, vital signs and ECGs, the assessment collected pre-dose on the first dose date will be defined as baseline; other assessments, including unscheduled or postdose assessments on the first dose date will not be defined as baseline.

Study day is defined as date of assessment – first dosing date + 1 for any assessment done on or after first dosing date; otherwise, study day is defined as date of assessment – first dosing date.

8.3 Imputation of Missing Data

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purpose, partial dates for adverse events, prior and concomitant therapies, disease diagnosis date, and start date of new anticancer therapy will be imputed if needed. Partial dates for laboratory values, vital signs, and ECGs will not be imputed.

The imputation rules will be specified in study analysis dataset specification with more details.

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 (TLGs) shells will be provided in a separate document, which will show the content and format of all the TLGs in details.

12 REFERENCES

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