STATISTICAL ANALYSIS PLAN

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Study Protocol Title:	An Open-Label Multicenter Phase 1 Study of E7046 in Subjects With Selected Advanced Malignancies
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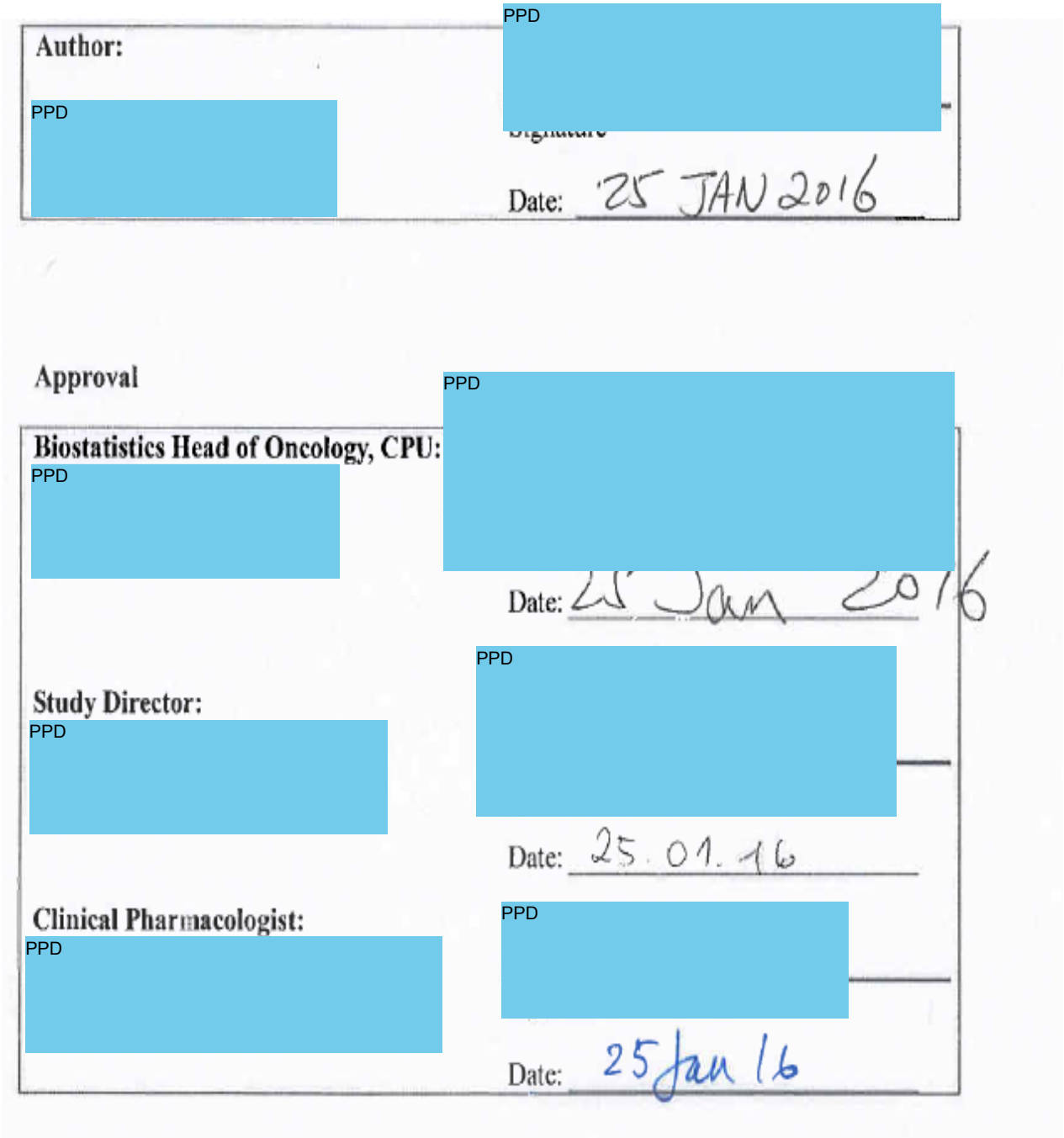
SIGNATURE PAGE



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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (TO BE ADDED)

Abbreviation	Term
AE	adverse event
ATC	anatomical therapeutic class
AUC	area under the concentration-time curve
BLQ	below limit of quantification
BMI	body mass index
BOR	best overall response
BSA	body surface area
CxDy	Cycle x Day y
CBR	clinical benefit rate
CI	confidence interval
CL	total body clearance
CLr	renal clearance
Cmax	maximum observed plasma concentration
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
FAS	full analysis set
fe	fraction excreted
^{18}FDG-PET	^{18}fluorodeoxyglucose positron emission tomography
irCR	immune-related complete response
irNE	(immune-related) not evaluable
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irRECIST	immune-related RECIST
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic
PFS	progression-free survival

PK	pharmacokinetic
PR	partially response
PT	preferred term
Q1	first quartile (25 percentile)
Q3	third quartile (75 percentile)
R2PD	recommended phase 2 dose
Rac	accumulation ratio
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease or standard deviation
SE	standard error
SI	Système International
SOC	system organ class
t1/2	terminal elimination half-life
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
tmax	time to maximum concentration
TTR	time to response
Vd	volume of distribution
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 Eisai Protocol E7046-G000-101 Amendment 01 dated 30 December 2015.

3.1 STUDY OBJECTIVES

3.1.1 Primary Objective(s)

The primary objectives of the study are to:

- Assess the safety/tolerability profile of E7046 as a single agent administered orally once daily, continuously in 21-day cycles, in subjects with selected advanced and/or recurrent malignancies.
- Determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of E7046.

3.1.2 Secondary Objective(s)

The secondary objectives of the study are to:

- Evaluate the pharmacokinetic (PK) profile of E7046.
- Evaluate the objective response rate (ORR) according to the immune-related RECIST (irRECIST) in subjects treated with E7046 with selected tumor types with high level of myeloid infiltrate.
- Evaluate the following additional efficacy endpoints according to the irRECIST: time to response (TTR), duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and clinical benefit rate (CBR).

3.1.3 Exploratory Objective(s)

The exploratory objectives of the study are to:

- Explore efficacy according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1, using the following endpoints: ORR, TTR, DOR, PFS, DCR, and CBR.
- Assess overall survival (OS).
- Explore the pharmacodynamic effect of E7046 on selected immune cell populations and selected biomarkers in tumor infiltrate and in peripheral blood.
- Explore ^{18}FDG-PET as a biomarker of response.
- Explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship.

3.2 OVERALL STUDY DESIGN AND PLAN

This is an open label, multicenter, Phase 1 study that will be conducted in 2 parts: a dose escalation part and a cohort expansion part. The objective of the dose escalation part is to assess the safety and tolerability and determine the MTD and/or RP2D of E7046. In the cohort

expansion part an additional 6 to 16 subjects will be treated at the RP2D to further characterize safety, efficacy, PK, and PD. E7046 is a novel cancer immune therapy and as this is the first study in humans therefore a cautious approach in the first cohort of patients is prudent. Staggered start of dosing in the first cohort will thus be implemented to ensure exposure of a limited number of subjects in the initial dosing cohort.

A major consideration was that the toxicities of E7046 are likely to be moderate in the dose range planned and an MTD may not be reached (according to preclinical results). It is anticipated that the RP2D will be selected based on integrated evaluation of safety, tolerability, clinical benefit, PK, and PD data, collected from all dose levels tested. Accordingly, a modification of the standard 3+3 design was selected, where dose cohorts of 6 subjects will be enrolled at each of the 4 dose levels to be tested so as to provide sufficient data for selecting RP2D in the absence of an MTD.

The study will consist of three phases for each subject: Pretreatment Phase, Treatment Phase, and Extension Phase.

A schematic of the 3 Phases is shown in Figure 1.

Figure 1 Study Design

PHASE	**Pretreatment** →		**Treatment** →			**Extension** →			
PERIOD	Screening	Baseline	Treatment Cycle 1			Treatment Continuation (Cycle 2 and beyond)		EOT	Follow -Up
Day	–28 to –1	-3 to -1	D1	D8	D15	D1	D8 (C2-6 only)		
VISIT	1	2	3	4	5	6, 8 etc	7, 9 etc	98	99

EOT = End of Treatment

The schedule of procedures/assessments for the study is presented in Section 13.1.

The study may be cut off for the data analysis and report when the study achieves its primary objective, i.e., the last subject completes his/her first cycle of study drug/treatment phase, or the sponsor and primary investigator of the study may determine the cutoff date for the analysis based on the enrollment and overall progress of the study.

4 DETERMINATION OF SAMPLE SIZE

The sample size of approximately 40 subjects is considered adequate for the purposes of selecting a dose.

The expected sample size for the dose escalation part of this trial will be up to 24 patients. Per the dose escalation design adopted and modified from the traditional 3+3 design, there will be a

maximum of 4 planned cohorts and there will be 6 subjects each cohort to allow for adequate assessment in tolerability, clinical benefit, PK, PD data and integrated evaluation of safety so as to select RP2D. Additional 6-16 subjects will be enrolled in the expansion cohort to confirm RP2D.

The dose escalation part and the extension part yield a total maximum sample size of 40 subjects.

5 STATISTICAL METHODS

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

5.1 STUDY ENDPOINTS

5.1.1 Primary Endpoint(s)

Primary Endpoints (Dose Escalation Part):

- Safety/tolerability profile of E7046.
- MTD and/or the RP2D.

5.1.2 Secondary Endpoint(s)

Secondary Efficacy Endpoints:

- Objective response rate (ORR)

  The ORR is the proportion of patients achieving a best overall response (BOR) of confirmed partial or complete response (irPR + irCR), according to the irRECIST (Section 13.2) from first dose date until disease progression/recurrence. 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.

- Duration of response (DOR)

  The DOR is defined as the time from the date of first documented confirmed irCR/irPR until the first documentation of confirmed disease progression or death, whichever comes first.

- Progression-free survival (PFS)

  The PFS is defined as the time from first dose date to the date of the first documentation of confirmed disease progression or death (whichever occurs first) using irRECIST. The PFS is also defined as the event that a subject is alive without confirmed disease progression at a specific evaluation time point. The censoring rule for events will be defined in the SAP.

- Disease control rate (DCR)

  The DCR is the proportion of patients achieving irPR + irCR + irSD from first dose date until disease progression/recurrence.

- Clinical benefit rate (CBR)

  The CBR is the proportion of patients achieving irPR + irCR + durable irSD [lasting at least 24 weeks] from first dose date until disease progression/recurrence.

5.1.3 Exploratory Endpoint(s)

Exploratory Endpoints:

- ORR, TTR, DOR, PFS, DCR, and CBR according to RECIST 1.1
- Assess overall survival (OS)
- Explore the pharmacodynamic effect of E7046 on selected immune cell populations and selected biomarkers in tumor infiltrate and in peripheral blood
- Explore 18FDG-PET as a biomarker of response
- Explore the pharmacokinetic/pharmacodynamic (PK/PD) relationship

5.2 STUDY SUBJECTS

5.2.1 Definitions of Analysis Sets

Full Analysis Set will include all subjects who received at least one dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics. This analysis set will also constitute the **Safety Analysis Set**.

DLT Evaluable Set will consist of those subjects who are evaluable for the DLTs (Section 13.3). This will be the analysis set for DLT analysis.

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

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

Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set will consist of all subjects in the Safety Analysis Set that also have evaluable serum PK and PD pretreatment assessment and at least 1 post treatment assessment.

Response Evaluable Set will consist of those subjects who have received at least 1 dose of study drug and have measurable disease at baseline and at least 1 post-baseline evaluation. This will be the primary analysis set for tumor response analysis.

FDG-PET Analysis Set will include all subjects with a baseline and at least one post baseline evaluable FDG-PET/CT assessment.

5.2.2 Subject Disposition

The number (percentage) of treated subjects will be summarized as well as subjects who completed the study/discontinued from the study and reasons for discontinuation by dose group.

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

The number of subjects who signed informed consent and the number (percentage) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition Case Report Forms (CRFs). Reasons for screen failure will also be listed.

5.2.3 Protocol Deviations

Protocol deviations are based on the selected inclusion, exclusion, and on-treatment criteria.

The major and minor protocol deviations will be finalized, documented and listed prior to database lock.

5.2.4 Demographic and Other Baseline Characteristics

The demographic and baseline characteristics will be summarized using descriptive statistics by dose group. Subject demography information will be collected at the Screening Visit.

Demographic and other baseline characteristics will be summarized using the Full Analysis Set, for each dose group and listed for each subject. For continuous demographic/baseline variables including age (year), height (cm), weight (kg), BMI (kg/m^2: weight[kg]/{height[m]×height[m]}), and BSA (m^2: height[cm]×weight[kg]/3600), 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, >65 years), race (White, Black or African American, Asian [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), and Eastern Cooperative Oncology Group (ECOG) performance status grade (0 - 5).

MEDICAL HISTORY

The number (percentage) of subjects reporting a history of any medical condition, as recorded on the Case Report Form (CRF), will be summarized for each dose group and overall. A subject data listing of medical and surgical history will be provided.

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 2015 version or later. The number (percentage) 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 (i) have started before the first dose of study drug and are continuing at the time of the first dose of study drug, or (ii) have started on or after the date of the first dose of study drug up to 30 days following the last dose.

A medication that cannot be determined as prior/concomitant due to missing/incomplete dates will be regarded as a concomitant medication.

Prior and concomitant medications will be summarized separately by anatomic class, pharmacological class, and WHO drug name (preferred term) by frequency counts and percentages.

Subject data listings will be provided for medications recorded during the study.

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

Not applicable.

5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

5.3.4 Examination of Subgroups

No subgroup analyses are planned for this study.

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

Adverse Events

An adverse event is defined as "treatment emergent" if it starts on or after the first dose date.

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

a. Date is completely missing; or
b. Year is missing; or
c. Day and month are missing and the year is equal to or after the year of the first dose date; or
d. Day is missing, and
   - the year is after the year of the first dose; or
   - 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.

Concomitant Medications

Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose.

Unless a medication is prior determined by the end date (i.e., end date is before the first dose) regardless the start date is partially or completely missing, medications with incomplete start and/or end date will be considered concomitant if:

a. Date is completely missing; or
b. Year is missing; or
c. Day and month are missing and the year is equal to or after the year of the first dose date; or
d. Day is missing, and
   - the year is after the year of the first dose; or
   - 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.

5.3.6 Other Considerations

There are no other specific considerations that are not covered in other relevant sections of this SAP.

5.4 EFFICACY ANALYSES

Tumor response will be assessed by both immune-related RECIST [irRECIST] and modified version of RECIST 1.1 criteria [Eisenhauer, 2009]. All efficacy analyses will be performed on the Response Evaluable Set.

5.4.1 Efficacy Analyses According to immune-related RECIST (irRECIST)

Tumor assessments and overall response to the treatment according to irRECIST are presented in Section 13.2. The confirmation of progressive disease (irPD) is required at least 4 weeks after the initial irPD. If irPD at two consecutive tumor assessment visits with less than 4 weeks, the additional confirmation of irPD visit is required. If irPD is confirmed, the documented start date of irPD is determined as follows:

1. The date of the initial irPD if it is confirmed on consecutive tumor assessment visits.

2. The date of the second irPD if the initial irPD is confirmed not on consecutive tumor assessment visits.

The best overall response (BOR) is defined as follows:

- **irCR**

  To achieve BOR of irCR, irCR must be observed at two consecutive tumor assessment visits with at least 4 weeks apart before the confirmed irPD, death, or end of study (whichever occurs first). If complete response at two consecutive tumor assessment visits with less than 4 weeks, the confirmation of irCR at the next assessment visit is required. The documented start date of irCR is defined as the date of the initial irCR.

- **irPR**

When BOR of irCR is not achieved, BOR of irPR can be achieved by that an initial irPR is confirmed by irPR or irCR at next consecutive visit (≥4weeks after the first irPR response). If irPR or irCR happens at two consecutive tumor assessment visits within 4 weeks, the additional confirmation of irPR (irPR or irCR in a later visit) is needed for BOR of irPR. The documented start date of irPR is the date of the initial irPR.

- **irSD**

If the documented start date of irPD is not the first evaluable tumor assessment visit after the first dose of study drug and the BOR is not a confirmed irCR/irPR, then the BOR is stable disease (irSD) when the duration of irSD is no less than 5 weeks. The duration of irSD is defined as the time from the first dose date to the documented start date of irPD, death, or the last evaluable tumor assessment (whichever occurs first).

- **irPD**

If the documented start date of irPD is the first evaluable tumor assessment visit after the first dose of study drug, then the BOR is irPD.

Table 1 listed general rules in the derivation of BOR with two consecutive tumor response results.

Table 1 Derivation of BOR with Two Consecutive Tumor Response Results

Timepoint 1 Initial Response	**Timepoint 2 Follow-up Response ≥ 4 weeks**	**BOR**
irCR	irCR	irCR
irCR	irPR/irSD/irPD	irSD/irPR*
irPR	irPR/irCR	irPR
irPR	irSD	irSD
irPR	irPD	irSD
irSD	irSD	irSD
irSD	irPD	irSD, provided minimum irSD duration met
irPD	irPD	irPD

*If an irCR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting irPR criteria relative to baseline, makes the disease irPD at that point (since disease must have reappeared after irCR). Best response would be irSD. However, sometimes 'irCR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had irPR, not irCR at the first time point. Under these circumstances, the original irCR should be changed to irPR and the best response is irPR.

- **irNE**

The BOR will be irNE in the following scenarios:

  - No evaluable tumor assessment
  - Only one evaluable tumor assessment with the result of either irPD or irCR/irPR/irSD but the duration of irSD is less than 5 weeks.

- **Handling of Missing /Not Evaluable Tumor Assessments**

The following rules will be used to handle missing and/or not evaluable tumor assessments:

  - One missing or not evaluable tumor assessment will be ignored if it is between two evaluable tumor assessments.
  - All the missing and/or not evaluable tumor assessments will be ignored if they are the only ones in between two irPDs. In this case, the irPD is confirmed and the documented start date of irPD is the date of the first irPD.
  - All the missing and/or not evaluable tumor assessments will be ignored if there is no evaluable tumor assessment after them.
  - Two irCRs, two irPR, or irPR and irCR with two or more missing and/or not evaluable tumor assessments in between will result in not evaluable result, i.e., irNE.

Objective Response Rate (ORR)

The objective response rate (ORR) is the proportion of patients achieving a best overall response of confirmed irPR or irCR according to irRECIST from first dose date until disease progression, death, or end of study (whichever occurs first). 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. The count and percentage for the ORR will be summarized by dose group.

Time to Response (TTR)

The time to response (TTR) is defined as the elapsed time (weeks) from the first dose date to the documented start date of confirmed irCR/irPR according to irRECIST. The descriptive statistics for the TTR will be summarized by dose group for the patients with the BOR of confirmed irCR/irPR.

Duration of Response (DOR)

The duration of response (DOR) is defined as the time (months) from the documented start date of confirmed irCR/irPR according to irRECIST until the documented start date of irPD or death (whichever occurs first).

For subjects with the BOR of irCR/irPR who did not die and had no documented progression before the cut-off date for the end of the study, or before early discontinuation (including discontinuations due to toxicity, undocumented clinical progression, change of cancer treatment, or decreasing performance status), and who died or progressed after more than one missed visit, will be censored on the date of their last assessment with the BOR of irCR, irPR or irSD.

The descriptive statistics (median and its standard error, Q1 and Q3) for the DOR will be summarized by dose group for the patients with the BOR of confirmed irCR/irPR using Kaplan-Meier method.

Progression-Free Survival (PFS)

Progression-free survival is defined as alive without confirmed irPD using irRECIST at the end of study or certain evaluation time points such as 3 months, 6 months, etc. The time for PFS is defined as the elapsed time from first dose date to the documented start date of irPD or death (whichever occurs first).

In analysis of PFS, the censoring rule is as follows:

- Subjects who did not die and had no documented progression (confirmed irPD) before the cut-off date for the end of the study, or before early discontinuation (including discontinuations due to toxicity, undocumented clinical progression, change of cancer treatment, or decreasing performance status), PFS will be censored on the date of their last evaluable assessment.
- Subjects who died or progressed after more than one missed visit, or non-evaluable assessment, or a combination of two, PFS will be censored on the date of their last evaluable assessment before the death or progression.

The rate for PFS will be summarized by evaluation time point and dose group. The time curve and median of PFS will be estimated and reported by the Kaplan-Meier method.

Disease Control Rate (DCR)

The disease control rate (DCR) is the proportion of patients achieving the BOR of confirmed irCR, confirmed irPR or irSD with the duration of at least 5 weeks. The count and percentage for the DCR will be summarized by dose group.

Clinical Benefit Rate (CBR)

The Clinical benefit rate (CBR) is the proportion of patients achieving the BOR of confirmed irCR, confirmed irPR or durable irSD (i.e., the duration of at least 24 weeks). The count and percentage for the CBR will be summarized by dose group.

5.4.2 Efficacy Analyses According to Modified RECIST 1.1 (mRECIST 1.1)

Modified RECIST 1.1 is the same as the RECIST 1.1 but allow to choose up to ten (10) target lesions and five (5) per organ at baseline instead of 5 target lesion (and 2 per organ) if clinically relevant via CT/MRI scans. In contrast to irRECIST, Modified RECIST 1.1 does not require the confirmation of progressive disease (PD).

The best overall response (BOR) based on mRECIST 1.1 is defined similarly as that according to the irRECIST (Section 5.4.1) except that the confirmation of PD is not required.

Objective response rate, time to response (TTR), duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and clinical benefit rate (CBR) according to modified RECIST 1.1 will be analyzed similarly to those according to irRECIST (Section 5.4.1).

5.4.3 Overall Survival (OS) Analyses

Overall survival rate will be presented at each evaluation visit by dose group. The survival (function) curve and median survival time will be estimated and reported by the Kaplan-Meier method.

5.4.4 FDG-PET Analyses

The change from baseline at Week 6 and Week 12 will be summarized by the descriptive statistics for the following FDG-PET/CT measurements:

- Sum of maximum for target lesions (Single pixel, unitless)
- Maximum SUV (single pixel, unitless)
- Maximum SUV (1 cm spot, unitless)
- Average metabolic SUV (unitless)
- Metabolic Volume (mm2)
- Total Tumor Volume (mm2)

The shift table from baseline for overall status of none-target lesions (present/absent) and status of new lesions (present/absent) will be tabulated at Week 6 and Week 12.

FDG-PET/CT as a biomarker of response analyses will be detailed in a separate biomarker analysis plan.

5.5 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Analyses

Plasma concentrations were obtained from blood samples drawn at each study visit during the treatment period (C1D1 and C1D8). Details of the analysis methods for population PK/PD modeling will not be described in this SAP but will be described in a separate analysis plan.

5.5.1 Pharmacokinetic Analyses

Blood samples for PK analyses will be collected during Cycle 1 on Day 1 and Day 8 at predose (0 h), 0.5, 1, 2, 4, 6, 8, and 10 and 24h postdose. Urine samples for PK analyses will be collected during the Dose Escalation part only Cycle 1.

Concentration data for E7046 and its major metabolite M1 will be analyzed and summarized by time point and dose group, respectively. Linear/semi-log plots of individual concentration data and mean concentration with SD over time will be presented for E7046 and its major metabolite M1 by dose group based on the pharmacokinetic analysis set.

For Cycle 1 on Day 1 and Day 8, PK parameters will be derived using non-compartmental methods for E7046 and its metabolite include, but are not limited to:

- maximum concentration (Cmax),
- time to maximum concentration (tmax),
- area under the curve from 0 to 24 hours (AUC0-24),
- area under the curve from 0 to infinity (AUC0-inf) ,
- elimination half life (t1/2); and if data permit,
- total body clearance (CL),
- volume of distribution (Vd),
- renal clearance (CLr),
- accumulation ratio (Rac),
- fraction excreted (fe),
- cumulative amount excreted in urine (Ae).

Descriptive statistics will be used to summarize PK parameters for E7046 and its metabolite by dose group based on the pharmacokinetic analysis set.

When presenting individual/raw values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, standard deviation [SD], and coefficient variation [CV]) will have 3 significant digits. For t1/2, raw values and median have fixed 2 decimal places.

In addition, plots of AUC, Cmax and CL versus dose as well as cumulative Ae versus time intervals (0-6 hours, 6-12 hours and 12-24 hours) will be presented for E7046 and its major metabolite M1 based on the pharmacokinetic analysis set.

5.5.2 Pharmacodynamic and Pharmacogenomic Analyses

Pharmacodynamics (PD) biomarkers including Proof of Mechanism (POM) biomarkers to show target engagement and Proof of Principle (POP) biomarkers to show impact of E7046 treatment on disease will be evaluated from collected samples.

Proof of Mechanism may be demonstrated by an alteration in expression of EP_4 response genes and/or proteins, as EP_4 is the molecular target of E7046.

POP for E7046 could be a change in intratumoral immune cell populations consistent with inhibition of EP_4 signaling such as a decrease in the ratio of M2/Total TAM or an increase in the number of CD8+ T cells. POP could also be a decrease in the number or ratio of MDSC in circulation.

Results from biomarker studies will be used to aid the selection of dose and for correlation with drug efficacy. The biomarker assessments planned for this study are summarized in Table 2.

Table 2 Biomarker assessments

Biomarker sample	Time points	Analyses	Potential Utility
Serum protein	C1D1 predose, 24hr after first dose, C1D8, C1D15	TAM/MDSC-related cytokines, eg, PGE_2, Renin)	POM
Serum mRNA	C1D1 predose, 24hr after first dose, C1D8, C1D15	Gene expression, eg, REN, EP_4	POM
Paired tumor biopsy	Predose and during Cycle 2	T cell and macrophage infiltration	POP
Archived tumor	Screening	To be decided	
Whole blood	Baseline, Predose on C1D1, C1D8, C1D15, C2D1, C3D1, and C5D1	Circulating MDSC	POP, POM, PS
Blood plasma	Baseline, time points for at each CT tumor assessment, and End of Treatment	Cell-free nucleic acid	
Whole blood DNA	Screening	Pharmacogenomic analysis	PG
Urine	Cycle 1 Day 1 pre-dose (0-hr) and Cycle 1 Day 1 and Day 8 post-dose to 6hr, 6 to-12hr, 12 to 24hr.	PGE_2 metabolite	POM

C1D1 = Cycle 1 Day 1, MDSC = myeloid-derived suppressor cell, PG = prostaglandin, PGE = prostaglandin e2, POM = Proof of Mechanism, POP = Proof of Principle, PS = patient stratification, REN = renin, TAM = tumor-associated macrophages.

Pharmacodynamic (PD), pharmacogenomic (PG) or other biomarker analyses will be detailed in a separate biomarker analysis plan.

5.6 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Set. Safety data will be presented by dose group (although there will be no formal statistical comparison in the safety analysis) and

will be summarized on an "as treated" basis using descriptive statistics (e.g., n, mean, SD, median, Q1, Q3, minimum, maximum for continuous variables; n (%) for categorical variables). Study Day 1 for all safety analyses is defined as the date of the first dose of study drug. Safety variables include treatment-emergent adverse events (TEAEs), 12-lead ECG results, clinical laboratory tests and vital signs. The incidence of TEAEs, clinical laboratory parameters and vital signs as well as their changes from baseline will be summarized using descriptive statistics. Abnormal values will be flagged.

5.6.1 Extent of Exposure

Number of cycles completed , duration of treatment and cumulative total dose will be summarized by dose group.

5.6.2 Dose Limiting Toxicity

After all subjects in a dose level tested complete the first treatment cycle, safety information for those subjects will be reviewed by the Eisai clinical team together with the principal investigator/s and dose limiting toxicity (Yes/No) and reason(s) (see Section 13.3) for experiencing a dose limiting toxicity (DLT) as well as date and dosage of study drug when the DLT occurred will be determined for each subject. This result will be listed for the study report.

5.6.3 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 18.0 or later. Adverse events will be coded to primary System Organ Class (SOC) and preferred term (PT) using MedDRA.

A treatment-emergent AE (TEAE) is defined as an AE that emerged during treatment (from first dose to 30 days after last dose of study drug) and

- had been absent at pretreatment (Baseline) or
- reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

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 within SOC and PT. Subjects will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT, and the subject will be counted with the worst grade for that particular AE. The number (percentage) of subjects with TEAEs will also be summarized by highest Common Terminology Criteria for Adverse Events (CTCAE) grade. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be possibly or probably related to study treatment. In summary, the following TEAE tables will be provided:

- Overview of TEAEs
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and CTCAE grade
- TEAEs with CTCAE grade 3 or 4 by SOC and PT
- TEAEs that led to drug discontinuation by SOC and PT
- TEAEs that led to dose reduction by SOC and PT
- TEAEs that led to dose interruption by SOC and PT
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs with CTCAE grade 3 or 4 by SOC and PT
- Treatment-emergent serious AEs by SOC and PT
- Treatment-related treatment-emergent serious AEs by SOC and PT

Subjects AE listings (treatment emergent or not) will be provided. In addition, the following subject AE listings will be provided:

- All fatal adverse events.
- All non-fatal serious adverse events (SAEs)
- All non-fatal non-serious treatment-emergent adverse events that led to discontinuation of treatment

5.6.4 Laboratory Values

Laboratory results will be summarized using the *Système international* (SI) units. Abnormal laboratory values will be identified as those outside the normal range. The abnormal values will be indicated in data listings.

On-treatment laboratory tests are defined as laboratory tests conducted from the start of treatment to no more than 30 days after the last dose of study treatment. Descriptive statistics for laboratory test results as well as change from baseline at each visit will be produced by visit and dose group.

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

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. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each post-baseline visit.

5.6.5 Vital Signs

Descriptive statistics for vital signs parameters (diastolic and systolic blood pressure, pulse rate, respiratory rate, and body temperature) and changes from baseline will be presented by dose group for each cycle and visit.

5.6.6 Electrocardiograms

The 12-lead ECG assessments were performed at specific visits (screening, baseline, Day 1 of each treatment cycle and off-treatment visit) as described in the protocol. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit and dose group.

The left ventricular ejection fraction (LVEF) from MUGA or Echocardiogram will be evaluated at baseline (Screening) and off-treatment visit. Descriptive statistics for changes and % change at off-treatment visit from baseline will be presented by dose group for each cycle.

Continuous Holter/ECGs will be collected during Cycle 1 on Day 1 and Day 8 at predose, and 0.5, 1, 2, 4, 6, 8 and 10 hours post dose. The analysis of continuous Holter/ECGs results will be included in a separate plan and therefore excluded in this plan.

5.6.7 Other Safety Analyses

No other safety analyses are planned for this study.

5.7 OTHER ANALYSES

Not applicable.

5.8 EXPLORATORY ANALYSES

The planned exploratory analyses are defined in Section 5.1.3 and detained in sections 5.4.2, 5.4.3 & 5.5.2. Additional exploratory analyses may be conducted if appropriate.

6 INTERIM ANALYSES

Not applicable.

7 CHANGES IN THE PLANNED ANALYSES

This SAP is in accordance with Clinical Study Protocol v1.0, dated 07 May 2015. No changes foe the planned analysis will be applied in this SAP.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

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

All by-visit analyses will be performed using assessments at corresponding scheduled visits recorded in the eCRF.

Partial dates for laboratory values, vital signs, and electrocardiograms (ECGs) will not be imputed.

Details on calculating pharmacokinetics parameters and the method to handle below limit of quantification (BLQ) values will be detailed in a separate plan.

When developing individual concentration-time profiles, BLQ values will be replaced with zero for the linear plot or missing for the semi-logarithm plot, respectively.

When calculating the mean or median value for the concentration 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.

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 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

1. Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009. 45(2): 228-47.

13 APPENDICES

13.1 Schedule of Procedures/Assessments

Table 3 Schedule of Procedures / Assessments in Study E7046-G000-101

	Phase	Pretreatment[a]		Treatment			Extension			
	Period	Screening	Baseline	Cycle 1			Treatment Continuation[b] (Cycle 2 and beyond)		Off-Treatment[c]	Follow-up[c]
	Visit	1	2	3	4	5	6, 8, etc.	7, 9, etc.	98	99
	Day	-28 to -1	-3 to -1	1	8	15	1	8 (C2-6 only)		
CRF	**Procedures/Assessments**									
S	Informed consent	X								
S	Inclusion/exclusion criteria	X								
S	Medical history	X								
S	Prior and concomitant medications	X		X	X	X	X	X	X	
S	Physical examination[d] and Vital signs[e]	X	X	X	X	X	X		X	
N	Echocardiogram / MUGA[f]	X							X	
S	Pregnancy test[g]	X	X	X			X			
S	ECOG performance status	X	X	X			X		X	
S	12-lead ECGs[h]	X	X	X			X		X	
S	ECG Holter monitoring[i]			X	X					
S	Hematology / Blood chemistry[j]	X	X	X	X	X	X	X	X	
S	Urinalysis[k]	X		X	X	X	X	X	X	
N	Genomic DNA[l]	X								
S	PK and PD urine collection[m]			X	X					
S	PK blood samples[n]			X	X					
N	PD blood samples[o]		X[o]	X	X[o]	X[o]	X[o]		X[o]	
N	Paired tumor biopsy and archived tumor[p]	X					X[p]			
N	^{18}FDG PET/CT[q]	X					X[q]			
S	Tumor assessments: CT or MRI[r]	X		Every 6 weeks or sooner if clinically indicated						
S	CT or MRI of the brain[s]			X						
N	Bone Scan[t]	X		Every 24 wks, or sooner if clinically indicated, and at confirmation of irCR						
S	E7046 administration[u]			Continuous daily dosing						
S	Adverse Events	X		X					X	
S	Survival status[v]									X

For CRF: S = standard assessment, N = nonstandard assessment (study-specific), N/A = not applicable.
AE = adverse event, β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, C1D1 = Cycle 1 Day 1, CR = complete response, CRF = case report form, CT = computed tomography, CTCs = circulating tumor cells, DNA = deoxyribonucleic acid, ECG = electrocardiograms, ECOG = Eastern Cooperative Oncology Group, ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, h = hour, HR = heart rate, irPR = immune-related partial response, irRECIST = immune-related RECIST, IV = intravenous, MDSC = myeloid-derived suppressor cell(s), MRI = magnetic resonance imaging, myeloid-derived suppressor cell, MUGA = multiple gated acquisition, PD =

pharmacodynamic, PGE2 = prostaglandin e2, PK = pharmacokinetic, PR = partial response, RECIST = Response Evaluation Criteria In Solid Tumors, RR = respiratory rate, SCCHN = squamous cell carcinoma of head and neck, SAE = serious adverse event, TNBC = triple-negative breast cancer.

a. The Screening Period extends from Day -28 to Day -1, except for signing of the informed consent form, which may be up to 8 weeks before the first dose of study drug. The baseline assessments may be performed from Day -3 to Day -1 (before the first dose of E7046). Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication.

b. The off-treatment assessment should occur within 30 days after the final dose of study treatment. Subjects who discontinue study for reasons other than disease progression will be followed until disease progression or death. All anticancer therapies will be collected (the sponsor may choose to stop the collection of therapies after the first anticancer treatment.

c. Visit windows are allowed from Cycle 3 onwards as follows: Day 1 (±3 days), and Day 8 (±3 days). There must be at least 5 days between the Day 1 and Day 8 visit for any given treatment cycle.

d. A comprehensive physical examination will be performed at the Screening Visit and at the Off-Treatment Visit. A symptom-directed physical examination will be performed on Day 1 of all treatment cycles and at any time during the study, as clinically indicated.

e. Vital signs include BP, HR, RR, and body temperature, as well as weight and height. BP, HR, and RR will be collected after the subject has been sitting for 5 minutes. Height will be measured at the Screening Visit only.

f. MUGA scans or echocardiograms will be performed at Screening, during the Off-Treatment Visit (window of ±1 week), and if clinically indicated. MUGA scans and echocardiograms will be performed locally in accordance with the institution's standard practice.

g. A serum pregnancy test (β-hCG) will be performed at screening for all premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A urine pregnancy test will be performed at baseline before the first E7046 dose, and on Day 1 of every Cycle.

h. 12-Lead ECGs will be collected at the following time points: Screening (single) and Baseline (single unless abnormalities are observed or if clinically indicated, then in triplicate at 2-minute intervals); Day 1 of all cycles (before and after study drug administration); and at the Off-Treatment Visit. In case of any alteration, or if clinically necessary, an echocardiogram and/or cardiac enzymes should be performed.

i. Continuous Holter/ECGs (12-h/12-lead) to be collected during Cycle 1 on Day 1 and Day 8 at predose (3 timepoints within 45 minutes), and 0.5, 1, 2, 4, 6, 8, and 12 h postdose. At each of these timepoints, patients should be supinely resting for at least 10 minutes prior to and 5 minutes after the nominal time. When coinciding, blood draws, vital signs and 12-lead safety ECGs should be performed immediately after the timewindow for ECG extraction..

j. Hematology and blood chemistry samples will be obtained before drug administration. Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication. Before drug administration on Cycle 1, Days 1 and 8, a complete blood count should be drawn.

k. Urine samples will be obtained before drug administration (either formal urinalysis or urine dipstick for protein and glucose are acceptable).

l. Genomic DNA samples will be collected predose at baseline. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

m. In Cycle 1, Day 1 and Day 8 All urine excreted will be collected as follows: pre-dose (0 hr), post-dose to 6hr, 6 to 12hr, 12-24hr. Total urine volume collected in each time interval will be recorded.Urine will be analyze for PK (E7046, M1 metabolite) and PD (PGE-M, metabolite of PGE2).

n. Blood samples for PK analysis will be collected in Cycle 1 on Days 1 and 8 at predose (0 h), 0.5, 1, 2, 4, 6, 8, 10, and 24h postdose.

o. Blood samples for PD mRNA and protein biomarker analysis (one red top serum tube and one PAX gene tube) will be collected at the following time points: predose (0 h) on Cycle 1 Day 1, 24 h after first dose, Day 8, and Day 15. Blood for cell free nucleic acid will be collected at C1D1 predose, at each tumor assessment, and at the end of treatment. Blood for MDSC in circulation will be collected at baseline, C1D1, C1D8, C1D15, C2D1, C3D1, and C5D1.

p. Paired tumor biopsies will be obtained, with appropriate subject consent. Subjects will have the biopsy before the first dose of E7046 and during Cycle 2, as long as the subject has had uninterrupted treatment at least 5 days prior to biopsy. In addition, archived fixed tumor tissue will be collected if available (instructions to be provided in a separate manual).

q. ^{18}FDG PET/CT scans should be performed according to instructions provided by the imaging core lab and sent to the core lab for quantitative assessments. Scans should be performed at baseline (within 7 days before C1D1) for all subejcts, Repeat scans in conjunction with the Week 6 and Week 12 tumor assessments timepoints only for subjects with evidence of evaluable FDG avid tumor lesion(s) at screening. ^{18}FDG-PET/CT scan timepoints may be changed based on emergent data.
Subjects must have a fasting serum glucose assessment performed before injection of the PET tracer for each scan. FDG-PET/CT will not be performed if serum glucose is >120 mg/dl for nondiabetics or >200 mg/dl for diabetic subjects.

r. Tumor assessments will be performed based on irRECIST and RECIST1.1. Treatment decisions will be based on irRECIST. Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks (during the 6th week; counting from C1D1) during treatment cycles in both the Treatment Phase and the Extension Phase. CT scans (with oral and intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1/ Day 1), using the above tumor assessment schedule, and as indicated clinically. Skin lesions may only be considered as non-index lesions (no photographs required) or as new lesions to add to the tumor burden sum. Subjects with SCCHN must also have head and neck scans performed at all tumor assessment timepoints.
MRI scans may be used instead of CT scans for (head, neck) abdomen and pelvis; however, chest must be assessed using CT. Chest disease may not be followed using chest x-ray. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be performed without IV contrast. The same method of assessment must be used at all time points as used at Screenin**g.**

s. Screening brain scans will be performed by MRI pre- and post- gadolinium or CT with contrast within 4 weeks prior to C1D1. During the Treatment Phase, CT/MRI of the brain will be performed if clinically indicated, and within a target of 1 week after a subject achieves a irCR. For subjects with history of treated brain metastases, brain scans will be performed at every tumor assessment time point. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability

t. A bone scan (99m-technetium polyphosphonate scintigraphy, whole body bone MRI, or 18F-NaF) to assess bone metastases will be performed within 6 weeks prior to C1D1 (historical scans are acceptable) and then every 24 weeks (within that 24th week) from C1D1 for tumor types known to metastasize to bone (eg TNBC, NSCLC etc.), or sooner if clinically indicated. In subjects whose body CT/MRI scans indicate irCR has been achieved, a bone scan will be required at confirmation of irCR to exclude new bone metastases. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure comparability. If a non-target lesion is being followed by bone scan (not present on CT/MRI), and is not imaged at a follow-up time point because a bone scan is not required at that time point, the time point non-target lesion response will be based upon the other non-target lesions and will not be considered not evaluable (NE).

u. E7046 should be taken daily at the dose assigned, with fasting 2 hours before and 2 hours after ingestion of E7046 capsules. On visit days, subjects should not take study medication before evaluations are performed.

v. Subjects who discontinue study will be followed for survival. Survival follow-up will be conducted approximately every 12 weeks on all subjects, unless they withdraw consent. Follow up on subsequent treatment and clinical response will be collected.

13.2 Adaptation of RECIST for Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Evalution Criteria in Solid Tumors (irRECIST)

Investigators should follow the guidelines provided here which are an adaptation of RECIST 1.1 and immume-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. Skin lesions are not permitted for selection as target lesions for this study.
- The ability to continue treatment, if clinically stable, until repeat imaging scans ≥ 4 weeks later (in most cases at the next scanning timepoint 6 weeks later) to confirm Progressive Disease (irPD)

Table 4 Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Evalution Criteria in Solid Tumors (irRECIST)

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 • 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 timepoints • 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 timepoints
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 non-liquid/non-necrotic 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 $_{\text{baseline}}$	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 timepoint SOD (SOD $_{\text{timepoint}}$). 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 between 5-10mm, actual diameter should be entered on 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
Non-Target Lesion Assessment	Non-target lesions are evaluated qualitatively as present, absent, not evaluable (NE) or unequivocal progression. The response of non-target lesions primarily contributes to the overall response assessments of irCR. Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even in the presence of stable disease or a partial response in the target lesion is indicative of irPD. irCR is not possible unless all non-target lesions are absent.

<table>
<tr><td>Definition of New lesion</td><td>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)</td></tr>
<tr><td colspan="2">3. irRECIST Overall Tumor Assessment</td></tr>
<tr><td>irCR</td><td>Complete disappearance of all measurable and nonmeasurable lesions (from baseline) and there are no unequivocal new lesions (unconfirmed irCR).
Lymph nodes must decrease to < 10 mm in short axis.
Confirmation of response is required ≥ 4 weeks later, preferably at next timepoint, to be considered a confirmed irCR.</td></tr>
<tr><td>irPR</td><td>If the $SOD_{timepoint}$ of TLs decreases by ≥ 30 % compared to $SOD_{baseline}$ and there are no unequivocal new lesions, and no progression of non-target disease, it is an irPR (unconfirmed).
Confirmation is required ≥ 4 weeks later, preferably at next timepoint, to be considered a confirmed irPR.</td></tr>
<tr><td>irSD</td><td>Failure to meet criteria for irCR or irPR in the absence of irPD.
If the sum of the TLs and the status of the non-target lesions do not reach the criteria to meet irPR or irPD (increase ≥20% and at least 5 mm absolute increase in SOD compared to nadir†) the response is irSD.
irSD = 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 timepoint from baseline onward.</td></tr>
<tr><td>irPD</td><td>Minimum 20% increase and a minimum 5 mm absolute increase in SOD compared to nadir, or irPD for non-target lesion(s) or unequivocal new lesion(s).
Confirmation of progression is recommended at a minimum of 4 weeks after the first irPD assessment (preferably at next tumor assessment timepoint).
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.
<table>
<tr><td></td><td colspan="2">Clinically Stable</td><td colspan="2">Clinically Unstable</td></tr>
<tr><td></td><td>Imaging</td><td>Treatment</td><td>Imaging</td><td>Treatment</td></tr>
<tr><td>1st radiologic evidence of PD</td><td>Repeat imaging at ≥ 4 weeks (next TA timepoint) to confirm PD</td><td>May continue study treatment at the Investigator’s discretion while awaiting confirmatory scans</td><td>Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only</td><td>Discontinue treatment</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Subsequent scan confirms PD</td><td>No additional imaging required</td><td>Discontinue treatment</td><td>No additional imaging required</td><td>N/A</td></tr><tr><td>Subsequent scan shows SD, PR or CR</td><td>Continue regularly scheduled imaging assessments</td><td>Continue study treatment at the Investigator's discretion</td><td>Continue regularly scheduled imaging assessments</td><td>May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion</td></tr></table> Subjects may continue receiving study treatment while waiting for confirmation of irPD 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 irPD is confirmed and the subject is experiencing extraordinary clinical benefit, site must contact Sponsor to discuss continuing treatment
irNE	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	irCR[¥]
↓100	Present/NE	Absent	irPR[¥]
↓≥30	Present/Absent/NE	Absent	irPR[¥]
↓<30 to <20↑	Present/Absent/NE	Absent	irSD
↓100 ↓≥30 ↓<30 to <20↑ NE	Present/Absent/NE	Present	irPD[¥]
↓100	Unequivocal	Any	irPD[¥]

↓≥30 ↓<30 to <20↑ NE	progression		
↑≥20 from nadir	Any	Any	irPD[¥]
NE	Present/Absent/NE	Absent	irNE[¥]

* Decreases assessed relative to baseline, including measureable lesions only.
[¥] Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

13.3 Dose-Limiting Toxicities

Dose-limiting toxicities (DLTs) are any of the following drug related toxicities (any toxicities considered related, probably related, or possibly related to E7046) occurring during Cycle 1 as judged by the investigator.

- Nonhematologic toxicity ≥ Grade 3 (except diarrhea, nausea and vomiting unless lasting >3 days despite optimal supportive care)
- Hematologic toxicity:
  - Grade 4 neutropenia for ≥ 5 days, or Grade 3 neutropenia with fever (fever is 38.4 ºC),
  - Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or lasting >7 days
- Any other toxicity assessed as related to E7046 treatment, and which in the opinion of a study investigator(s) the sponsor physician constitutes a dose-limiting toxicity
- Subjects who have missed > 4 days of dosing in Cycle 1 due to drug-related toxicity (but not qualifying for a DLT) will be assessed as experiencing a DLT.

Grading of toxicities is based on National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 (Section 13.4).

Adverse events occurring after Cycle 1 may be considered DLTs upon discussion between the investigator and the sponsor physician.

The following toxicities will not be considered DLTs:

- Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor)
- Grade 3 immune-related adverse event (irAE) that resolves to ≤ Grade 1 within 7 days
  - An irAE, a subset of AEs, is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and

histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Subjects who do not complete at least 17 of 21 days of dosing in Cycle 1 due to reasons other than treatment related toxicity will be replaced for the purpose of DLT evaluation.

Assessment of DLTs will be discussed and agreed to by investigator(s) and sponsor physician prior to proceeding to the next dose level, and the decision will be documented.

13.4 Common Terminology Criteria for Adverse Events (v4.03)

The National Cancer Institute's *Common Terminology Criteria for Adverse Events* (CTCAE v4.03 published 28 May 2009; v4.03: June 14, 2010) provides descriptive terminology to be used for AE 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 AE terms in CTCAE version 4.03 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA®) terms.

CTCAE v4.03 grading refers to the severity of the AE. CTCAE Grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Table 5 Common Terminology Criteria for Adverse Events v4.03 Grading

Grade	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.

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.
Source: Cancer Therapy Evaluation Program, NCI. CTCAE v4.03. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

For further details regarding MedDRA, refer to the MedDRA website: http://www.meddramsso.com.

CTCAE v4.03 is available online: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.