16.1.9 Documentation of Statistical Methods

Listed below are all versions of the Statistical Analysis Plan for this study. The corresponding documents are provided on the following pages.

Statistical Analysis Plan	Version	Date
Revised original	V2.0	25 MAR 2025
Original	V1.0	06 APR 2018



STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7130-J081-101
Study Protocol Title:	A phase 1 study of E7130 in subjects with solid tumors
Date:	25 Mar 2025
Version:	Version 2.0

REVISION HISTORY

The table below describes major revisions in version 2.0

Date: 25 Mar 2025

Section	Highlights of Major Changes/ Reason for Revision
3 and 4	Descriptions were updated following the latest Protocol.
5 and relevant sections	Group for summary in Part 2 was updated to follow updated study design.
5.1.2 and 5.4	Duration of response and time to to response were added as endpoints and analysis item
5.2.2	Format of subject disposition table was update.
5.2.3	The wording of major deviations was replaced to important deviations. Subject data listing was added.
5.2.4	Baseline characteristics newly defined in protocol amendments are added.
5.3.4	It was clarified that subgroup analysis is not performed.
5.4.1	It was clarified that swimmer plot, waterfall plot, and a combined figure is presented separately. Horizontal axis for swimmer plots was changed from PFS to duration of response.
5.4.1	Summary of survival follow-up time was added.
5.4.1	Censoring rule for overall survival was made clearer.
5.5	PK analyses using E7130 concentrations in feces and urine samples between 0-168 hour in Part 1 were deleted due to protocol amendment (version 6.0).
5.5.1	Not PK Analysis Set but the Safety Analysis Set will be used for the listings for PK analyses.
5.5.1	Descriptions about data not included in PK analysis and in calculation of summary statistics were added.
5.5.1	Descriptions regarding the handling of E7130 plasma concentrations when calculating PK parameters were added.
5.5.1	For summary statistics, infusion time category was added.
5.5.1	PK parameters to be calculated have been changed in Part 1.
5.5.1	Listing of E7130 plasma concentration in Part 2 was added.
5.5.1	The details of how to create the listings, tables and plots of concentrations and PK parameters of E7130 were changed in Part 1.
5.5.2	Analysis of blood PD marker analysis were planned.

5.5.3	Statistical analysis plan with plasma E7130 concentration-QTc were deleted because the analysis will be prepared in another cardiac statistical analysis plan.
5.5.1 and 8.4	Manual number of non-compartmental analysis was revised from 302-104.00 to 302-104.01.
5.6.1	Dose skip was defined and will be summarized.
5.6.1	Definition of dose delay was updated.
5.6.2	Table for non-serious TEAEs was added.
5.6.2	Table for COVID-19 related TEAEs was added.
5.6.2	Weight for PAVA was change to inverse of variance
5.6.5	Analysis for ECG was updated to follow Protocol Amendment.
5.6.6	Listing for potential Hy's law case was added
8.3	Analysis window for summary of safety parameters were replaced to VISIT in CRF.

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
ATC	anatomical therapeutic chemical
$AUC_{(0-inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$AUC_{(0-t)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
BC	breast cancer
BLQ	below the limit of quantification
BOR	best overall response
BSA	body surface area
CBR	clinical benefit rate
CI	confidence interval
CL	total clearance
C_{max}	maximum observed concentration
CR	complete response
CRC	coloreactal cancer
CRF	case report form
CSR	clinical study report
CTCAE	common toxicity criteria for adverse events
CV	coefficient variation
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GC	gastic cancer
Her2	human epidermal growth factor receptor type2
HPD	highest posterior density
HPV	human papillomavirus
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximally tolerated dose
mTPI	modified toxicity probability interval

Abbreviation	Term
NE	not evaluable
ORR	objective response rate
OS	overall survival
PAVA	pooled adjacent violators algorithm
PD	pharmacodynamics
PD	progressive disease
PFS	progression free survival
PGx	pharmacogenomics
PK	pharmacokinetics
PR	partial response
PS	performance status
PSN	peripheral sensory neuropathy
PT	preferred term
QT	QT interval
Q1	first quartile
Q3	third quartile
RD	recommended dose
RECIST	response evaluation criteria in solid tumor
SAE	serious adverse event
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SD	standard deviation
SD	stable disease
SI	système international
SOC	system organ class
SpO_2	percutaneous oxygen saturation
$t_{½}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TLG	tables, listings, and graphs
t_{max}	time at which the highest drug concentration occurs
TTR	Time to response
UC	urothelial carcinoma
UPM	unit probability mass
V_{ss}	volume of distribution at steady state

Abbreviation	Term
WHO DD	World Health Organization drug dictionary
λ_z	terminal phase rate constant

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 E7130-J081-101.

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the tolerability and safety profile of E7130 in subjects with advanced solid tumors.

3.1.2 Secondary Objectives

- To determine the maximally tolerated dose (MTD) of E7130 (only in Part 1).
- To evaluate the pharmacokinetics (PK) of E7130.
- To determine the recommended dose (RD) for future studies.
- To evaluate objective response rate (ORR), disease control rate (DCR) and clinical benefit rate (CBR).
- To evaluate progression-free survival (PFS), duration of response (DOR) and the overall survival (OS) (only in Part 2).

3.1.3 Exploratory Objectives

CCI

[redacted]

3.2 Overall Study Design and Plan

3.2.1 Overall Study Design and Plan

This is a Phase 1 study of E7130 in subjects with advanced solid tumors. This study will be conducted in 2 parts (Part 1 and Part 2). Part 1 will be the dose escalation portion of this study to assess dose-limiting toxicity (DLT) and to determine the MTD in subjects with solid tumors. Based on the efficacy, safety, PK and biomarker data in Part 1, 480 $\mu g/m^2$ every 3 weeks regimen was chosen for Part 2 [Protocol amendment 05]. Based on the safety data observed in the first 8 subjects treated in Part 2 at 480 $\mu g/m^2$ starting dose every 3 weeks, the starting dose was further reduced to 410 $\mu g/m^2$ every 3 weeks. The starting dose may be

reduced further to 350 μg/m^2 every 3 weeks based on the safety data of the first 10 subjects in Part 2 at 410 μg/m^2 every 3 weeks. The criteria for the further starting dose reduction are the occurrence of ≥Grade 3 peripheral sensory neuropathy (PSN) and/or ≥Grade 3 ileus which is considered to be related to neuropathy in 3 subjects or more out of the first total 10 subjects of both cohort 1 and 2 in the first 2 cycles. Based on the totality of the safety data observed in the first 2 cycles at 410 μg/m^2 every 3 weeks regimen, the Sponsor and Principal investigator(s) might decide to further reduce the starting dose to 350 μg/m^2 every 3 weeks. To ensure the safety of each subject, the Sponsor and Principal investigator(s) monitor the safety data closely, and the AEs will be assessed in ongoing basis. In addition, if complete response (CR) or partial response (PR) in tumor assessment is observed in 2 subjects or more out of 10 subjects in one initial dose level of cohort 2 (UC cohort), additional 20 subjects will be enrolled in this cohort. CR and PR must be confirmed by another scan in 4 weeks or later from the first observation [Protocol amendment 07]. Part 2 will comprise cohort expansions to further characterize the safety and tolerability of E7130 and to evaluate preliminary efficacy of E7130 in subjects with squamous cell carcinoma of the head and neck (SCCHN) and urothelial carcinoma (UC). RD for future studies will be determined based on the data from Part 1 and Part 2.

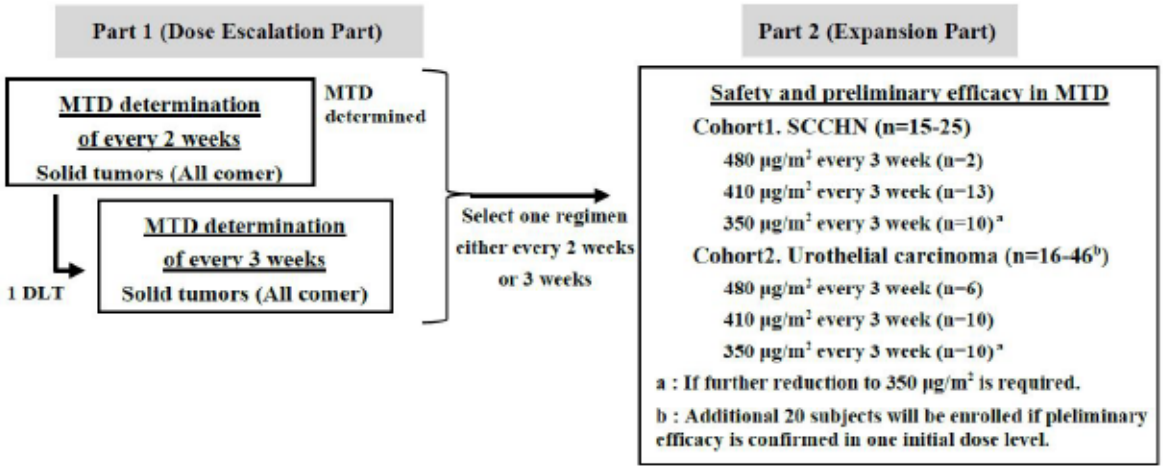


Figure 1 Overview of Study Design

3.2.2 Part 1

The study design overview of Part 1 is presented in Figure 2. Part 1 will be conducted in subjects with solid tumors. Part 1 will consist of a Pretreatment Phase, Treatment Phase, and Follow-up Phase.

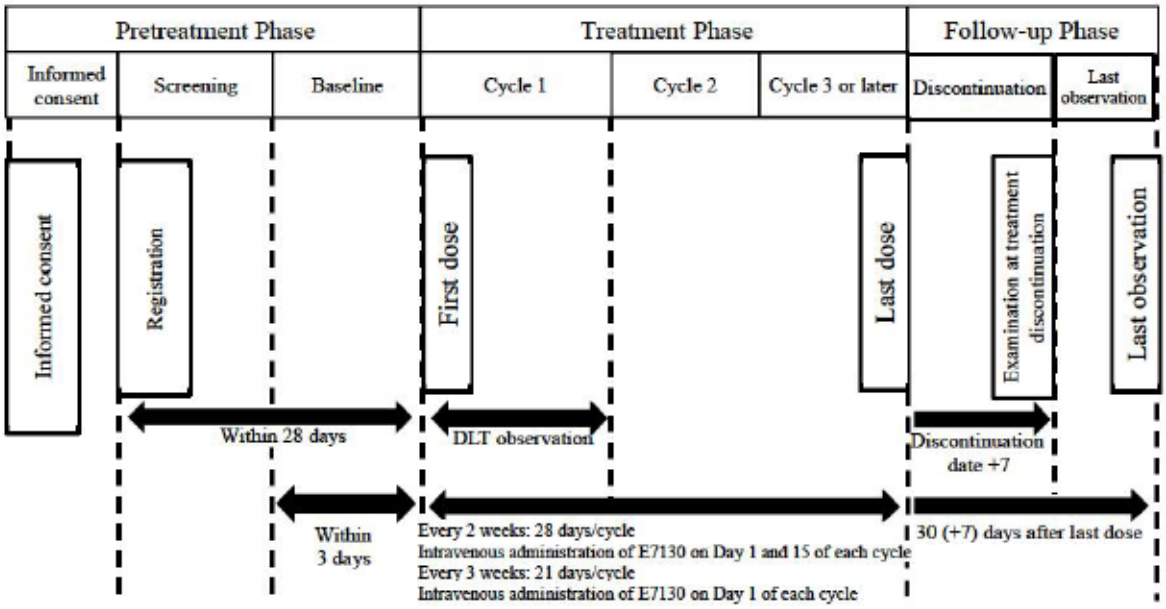


Figure 2 Overall Study design of Part 1

The Pretreatment Phase will involve obtaining informed consent, a screening period, and a baseline assessment. The Treatment Phase will consist of Cycle 1 for DLT assessment with every 2 weeks and every 3 weeks regimen and subsequent cycles for sequence treatment. First, DLT assessment will be initiated to determine MTD with every 2 weeks. Once the first DLT with every 2 weeks regimen is observed, DLT assessment will be initiated to determine MTD with every 3 weeks at (-1) lower dose than the dose where the first DLT with every 2 weeks regimen was observed. Based on result of DLT assessment including PK profile with every 2 weeks regimen, DLT assessment with every 3 weeks regimen may be shifted before the first DLT with every 2 weeks regimen is observed. For Cycle 1 and onward, each cycle is 28 days long for every 2 weeks regimen and 21 days long for every 3 weeks regimen. In Cycle 1 and onwards, subjects will be administered E7130 every 2 weeks (Day 1 and 15 of each cycle) or every 3 weeks (Day 1 of each cycle) until they meet any of the criteria in "Criteria for discontinuation" of study protocol. The Follow-up Phase will consist of the examination at study discontinuation and the last observation period.

Dose assignment of subjects

An accelerated Modified Toxicity Probability Interval (mTPI) design (Ji Y and Wang SJ, 2013) will be employed to determine the MTD of E7130. Firstly, MTD of E7130 with every 2 weeks regimen will be determined in following manner. The initial dose level of E7130 with every 2 weeks regimen will be 25 $\mu g/m^2$ and the first cohort would enroll 3 subject for DLT evaluation. In the first cohort only, initial administration of E7130 for the second subject must be started on and after the 29th day after C1D1 of the first subject. If drug-related Grade 2 or higher toxicity is observed in 1 or more subjects within the initial cohort, dose assignment for following cohorts will be determined based on mTPI design, described below. If drug-related Grade 2 or higher toxicity is NOT observed in the initial cohort, DLT will be evaluated in successive dose level with single-subject until such a toxicity was observed. If such a toxicity

is observed, the cohort will be expanded to enroll total 3 subjects.

After that, each subject will be assigned a dose of E7130 in accordance with the rules of the mTPI design based on a DLT rate of 25% and the corresponding 3 toxicity probability intervals that are defined as 20% to 30% (proper dosing), 0% to <20% (underdosing) and >30% to 100% (overdosing). The entire dose assignment decision rule can be precalculated under the mTPI design and presented in Table 1.

Table 1 Decision Rule for Dose Assignment

		Number of Evaluable Subjects at the Current Dose				
		3	6	9	12	15
Number of Subjects with DLT	0	**E**	**E**	**E**	**E**	**E**
	1	**S**	**S**	**E**	**E**	**E**
	2	**D**	**S**	**S**[a]	**S**	**E**
	3	**D, U**	**D**	**S**	**S**[a]	**S**[a]
	4		**D, U**	**D**	**S**	**S**[a]
	5		**D, U**	**D, U**	**S**	**S**
	6		**D, U**	**D, U**	**D, U**	**S**
	≥7			**D, U**	**D, U**	**D, U**

E = Escalate to the next higher dose, **S** = Stay at the current dose, **D** = De-escalate to the next lower dose [b], **U** = Current dose is unacceptably toxic (ie, Do not re-enter the current dose)

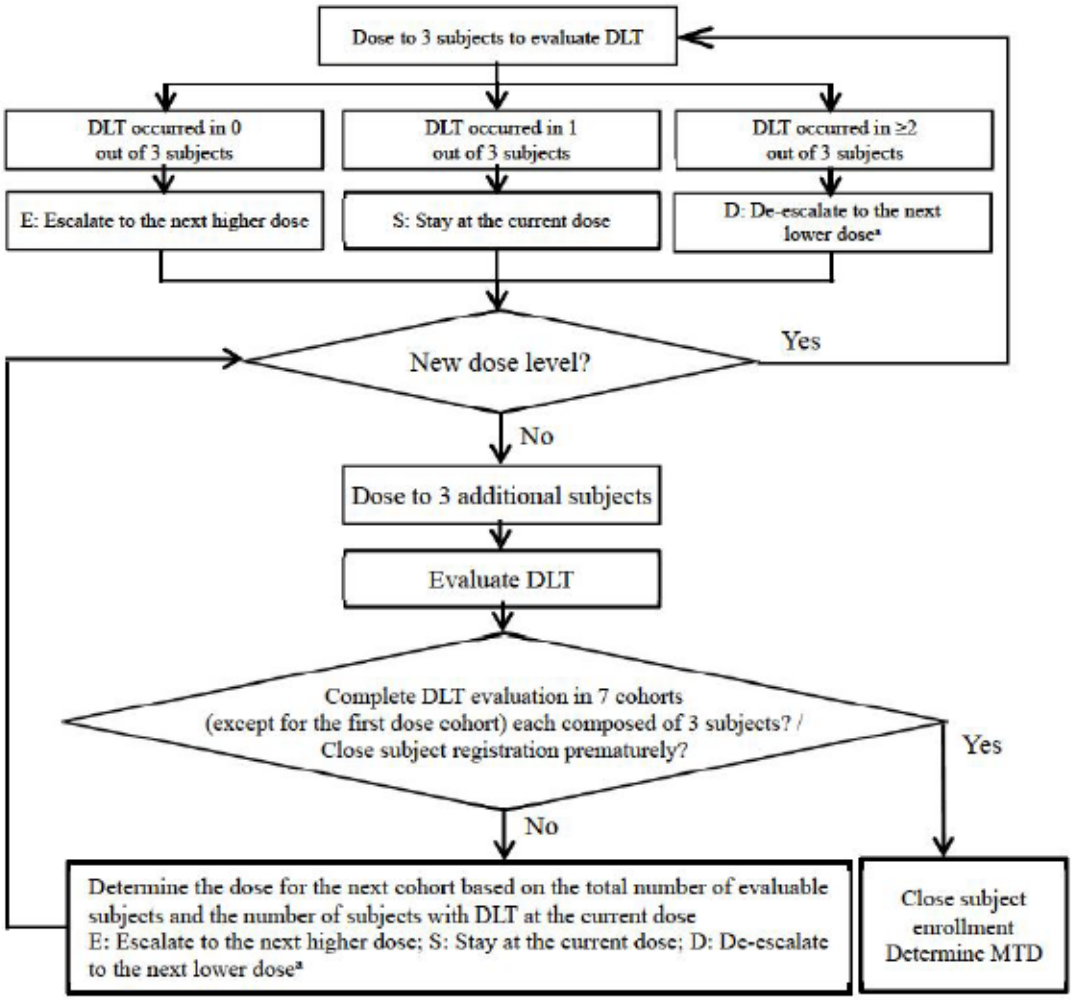
Target DLT rate at MTD = 25%, its equivalence toxicity interval = 20 to 30%, Cohort size = 3 subjects

Display for more than 15 subjects at the current dose is omitted

a: Early MTD determination and initiation of exploring OBD candidate may be considered.

b: If a 100% or 50% dose escalation resulted in "D", then an intermediate dose level between pre- and post-dose escalation would be evaluated in the next cohort.

Based on the number of subjects developing DLT(s) during the DLT assessment period in each dose level, dose assignment (escalate, stay, de-escalate) for the next 3 subjects will be determined according to the above table. When 1 subject has already been evaluated in next dose, two subjects will be enrolled and dose assignment will be determined based on a result from the 3 subjects. In case where 4 or more subjects were enrolled and evaluated in a cohort, dose assignment (not shown in above table) will be determined by a result from all the subjects at the dose. Next cohort at the dose level will enroll and evaluate 2 or less subject so that the number of subjects at the dose level be multiples of 3. For example, if 4 subjects are treated and evaluated at once as 1 cohort and another cohort is assigned to the same dose, 2 subjects will be treated and evaluated as the another cohort. At the new dose level where 3 subjects (except for initial dosing cohort of every 2 weeks regimen) are enrolled, the second subject should start to receive the initial administration of E7130 on the following day after the first subject is observed in C1D1. Subjects who are not evaluable for DLT (for example, those subjects who discontinued during Cycle 1 for reasons other than DLT occurrence) should be replaced within their dose level. When DLT evaluation is completed in 7 cohorts being composed of 3 subjects (except for initial dosing cohort), MTD for every 2 weeks regimen will be determined. However, the maximum number of the cohort may be adjusted as required. Details of the mTPI design are described in Section 5.3.6. Figure 3 shows the process of dose assignment to subjects based on Table 1.



a: If a 100% or 50% dose escalation resulted in "D," an intermediate dose level between the current dose and the next lower dose will be evaluated in the next cohort.

Figure 3 The Process of Dose Assignment

MTD in every 2 weeks regimen will be selected as the dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate based on the posterior distribution of DLT rate for each dose. Once MTD is selected in accordance with that way, we will finally determine MTD after toxicity data until Cycle 2 is taken into account. Once the first DLT with every 2 weeks regimen is observed, DLT assessment will be initiated to determine MTD with every 3 weeks at (–1) lower dose than the dose where the first DLT with every 2 weeks regimen was observed. Based on result of DLT assessment including PK profile with every 2 weeks regimen, DLT assessment with every 3 weeks regimen may be shifted before the first DLT with every 2 weeks regimen is observed. The initial dose level of E7130 with every 3 weeks regimen will be decided based on safety profile in every 2 weeks regimen and the first cohort would enroll 3 subjects for DLT evaluation.

The dose assignment rule in every 3 weeks regimen is also determined by mTPI method, described above. To determine dose assignment in every 3 weeks regimen, the DLT evaluation result at a same dose level in every 2 weeks regimen will not be pooled. When DLT evaluation is completed in 5 cohorts being composed of 3 subjects, MTD for every 3 weeks regimen will be determined in the same step as every 2 weeks regimen. However, the maximum number of the cohort may be adjusted as required.

If there are subjects who could not complete infusion of E7130 on C1D1 and C1D15 (only every 2 weeks regimen) or the DLT assessment during 28 days (every 2 weeks) / 21 days (every 3 weeks) period following first dose of E7130 because of any reasons except DLTs, the sponsor should discuss whether the subjects should be included in the DLT analysis population with the investigator, medical expert and if necessary, independent medical advisors. And based on the discussion, the sponsor could also replace DLT evaluable subjects enrolling additional subjects. In addition, transition to next dose levels and dose escalation range will be decided after also considering the safety data of those subjects who were excluded from the DLT analysis population.

Determination of dosage for Part 2

When MTD of one schedule regimen is determined, the sponsor may be able to decide the schedule regimen for Part 2 and start the enrollment in Part 2 cohort, based on the totality of preclinical and clinical information.

<Protocol Amendment 05>

It was determined that the schedule regimen for Part 2 is every 3 weeks (480 μg/m^2).

3.2.3 Part 2

Part 2 will consist of 2 cohorts. Subjects in each cohort will be enrolled in parallel. The subject will be enrolled at MTD of one schedule either every 2 weeks or 3 weeks selected in Part 1 (MTD of every 3weeks regimen (480 μg/m^2) is chosen for Part 2 [Protocol amendment 05]. Based on the safety data observed in the first 8 subjects treated in Part 2 at 480 μg/m^2 starting dose every 3 weeks, the starting dose was further reduced to 410 μg/m^2 every 3 weeks. The starting dose may be reduced further to 350 μg/m^2 every 3 weeks based on the safety data of the first 10 subjects in Part 2 at 410 μg/m^2 every 3 weeks. The criteria for the further starting dose reduction are the occurrence of ≥ Grade 3 PSN and/or ≥ Grade 3 ileus which is considered to be related to neuropathy in 3 subjects or more out of the first 10 subjects in the first 2 cycles. Based on the totality of the safety data observed in the first 2 cycles at 410 μg/m^2 every 3 weeks regimen, the Sponsor in collaboration with the Principal Investigator(s) might decide to further reduce the starting dose to 350 μg/m^2 every 3 weeks. To ensure the safety of each subject, the Sponsor and Principal investigator(s) monitor the safety data closely, and the AEs will be assessed in ongoing basis. In addition, if CR or PR in tumor assessment is observed in 2 subjects or more out of 10 subjects in one initial dose level of cohort 2 (UC cohort), additional 20 subjects will be enrolled in this cohort. CR and PR must be confirmed by another scan in 4 weeks or later from the first observation. [Protocol amendment 07]. In cohort1, subject with SCCHN will be enrolled, and consists of 15-25 subjects. In cohort2, subjects with urothelial carcinoma will be enrolled, and consists of 16-46 subjects.

Part 2 will consist of a pretreatment phase, a treatment phase, and a follow-up phase. The pretreatment phase will involve obtaining informed consent, a screening period, and a baseline assessment. The treatment phase will consist of treatment cycles that is 21 days (3weeks regimen) in duration, and administration of E7130 every 3 weeks will continue until subjects meet any of the criteria in "Criteria for discontinuation". The follow-up phase will consist of the examination at study discontinuation, the final observation and the follow-up for OS. In the follow-up for OS, subject's survival and post-anti-cancer treatment will be followed every 6 months until 18 months after the last subject enrollment, and if requested by the sponsor.

4 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to evaluate the tolerability and safety profile of E7130. The number of subjects in the Part 1 will be approximately 40. For every 2 weeks regimen, if drug-related Grade 2 or higher toxicity is not observed in 3 subjects at initial dosing cohort, some subjects will be enrolled in single-subject cohort and then 7 cohorts of 3 subjects (except for initial dosing cohort in biweekly regimen) will be investigated after increasing of cohort size from 1 to 3. Five cohorts of 3 subjects will be investigated in dose finding of every 3 weeks regimen. The maximum number of the cohort in mTPI parts may be adjusted if necessary. The maximum sample number of cohort for each regimen was deemed appropriate to explore some dose levels around MTD, and evaluate their safety profile.

The number of subjects in each cohort of Part 2 were mainly based on the feasibility of enrollment. This number of subjects will offer further evaluation for safety, preliminary efficacy and exploration of biomarker also. For cohort 1, 15 subjects with SCCHN will be enrolled. For cohort 2, 16 subjects with urothelial carcinoma will be enrolled initially. Additional 20 subjects will be enrolled when efficacy results from 10 subjects in an initial dose level meet the criteria described in interim analysis section to allow further investigation of safety and efficacy.

5 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the data cutoff for analysis or the study is completed and the database is locked. Statistical analyses will be performed using SAS software or other validated statistical software as required.

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

All statistical analysis will be performed by part separately. Every 2 weeks and 3 weeks regimen are not pooled on summarization in Part 1 but summarized separately.

As for Part 2, statistical analysis will be performed in following groups for each analysis item. A: 410 μg/m^2 in SCCHN, B: 480 μg/m^2 in SCCHN, C: 410 μg/m^2 in UC, D: 480 μg/m^2 in UC. Mark of plus stands for data pooling.

- Section 5.2.1, 5.2.2, 5.2.4, 5.2.5: A, B, A+B, C, D, C+D, A+C, B+D, A+B+C+D
- Section 5.4: A, B, C, D
- Section 5.5: As descrive there.
- Section 5.6: A, B, A+B, C, D, C+D, A+C, B+D, A+B+C+D

Note: Subjects were enrolled in 410 μg/m^2 and 480 μg/m^2 in SCCHN and UC cohorts.

The results of other biomarker analyses will be reported separately, and the details of these analyses will be described in a separate analysis plan.

5.1 Study Endpoints

5.1.1 Primary Endpoints

- **Tolerability endpoint:** DLTs.
- **Safety endpoints:** AEs, clinical laboratory tests, vital signs, arterial oxygen saturation, body weight, 12-lead ECGs, and ECOG PS.

5.1.2 Secondary Endpoints

- **MTD determination:** will be selected as the dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate based on the posterior distribution of DLT rate for each dose. Toxicity data until Cycle 2 is taken into account to finally determine MTD.
- **Pharmacokinetic endpoints:** The endpoints are PK parameters derived by noncompartmental analysis using the plasma concentration–time data of E7130, including followings but not limited to: maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), area under the concentration–time curve (AUC), terminal elimination phase half-life ($t_{1/2}$), total clearance (CL), and

distribution volume (V_d). The amount of unchanged drug excreted in urine and renal clearance(CL_R) will be derived, if possible in subjects who have urine samples in Part1.

- **RD:** The RD will be selected based on the MTD, efficacy, safety, PK profile and biomarker data in Part 1 and Part 2.
- **Efficacy endpoints:** Best overall response (BOR) based on RECIST 1.1, ORR, DCR, CBR, PFS, DOR, OS and percent changes from baseline in the sum of the diameters of tumor target lesions (if applicable). Time to response (TTR) will also be calculated and presented.

BOR is complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), and not evaluable (NE), where SD has to be achieved at ≥5 weeks after first dose. CR or PR in Part 1 of this study requires no confirmation of the subsequent response at ≥4 weeks. The confirmation is mandatory in Part 2. It is accepted there is one NE between two CRs for the confirmation of CR, one SD or NE between two PRs, or between PR and CR for the confirmation of PR.

ORR is defined as a proportion of subjects with BOR of CR or PR.

DCR is defined as the proportion of subjects with BOR of CR, PR or SD.

CBR is defined as the proportion of subjects with BOR of CR, PR or durable SD (duration of SD ≥ 23 weeks). Duration of SD is defined as the time from the date of first dose to the date of the first documentation of disease progression or death from any cause, whichever occurs first. Same censoring rules as PFS will be applied to calculate duration of SD. It will be calculated for subjects whose BOR is SD.

PFS is defined as the time from the date of first dose to the first documented date of event (disease progression or death from any cause, whichever occurs first).

DOR is defined as the time from the date of first documented date of CR or PR to the first documented date of event (disease progression or death from any cause, whichever occurs first). DOR will be calculated for subjects whose BOR is PR or CR.

OS is defined as the time from the date of first dose to the date of death from any cause. For the subjects who are alive or unknown, OS is censored as the date of last known alive date or the date of data cut off, whichever comes first.

TTR is defined as the time from the date of first dose to the date of first documented date of CR or PR. TTR will be calculated for subjects whose BOR is PR or CR.

5.1.2.1 Pharmacokinetic (PK) Endpoints

PK parameters derived by non-compartmental analysis using plasma and urine concentrations of E7130 which include, but are not limited to, are shown as below:

<Plasma PK Parameter>

Cycle 1 Day 1 and Cycle 2 Day 1

C_{max}	maximum observed concentration
t_{max}	time at which the highest drug concentration occurs
$AUC_{(0-t)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
$AUC_{(0-inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$t_{½}$	terminal elimination phase half-life
CL	total clearance
MRT	mean residence time
λ_z	terminal phase rate constant
V_{ss}	volume of distribution at steady state

Cycle 1 Day 15, Cycle 2 Day 15 (2 weeks regimen only), and Cycle 3 or later

C_{max}	maximum observed concentration

<Urinary PK Parameter>

$A_{e(0-t)}$	amount of unchanged drug excreted in urine up to time of last quantifiable urinary concentration (after dosing at time 0)
$A_{e(0-x)}$	amount of unchanged drug excreted in urine up to fixed time of x (after dosing at time 0)
$A_{e(t1-t2)}$	amount of unchanged drug excreted in urine between 2 data points t_1 and t_2
Fe	fraction of dose excreted in urine

5.1.3 Exploratory Endpoints

CCI

[redacted]

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The DLT Analysis Set is the group of subjects in the Part 1 who completed Cycle 1 treatment of the study drug and were evaluated for DLT, and those who developed DLT during Cycle 1. This will be the analysis set for MTD determination in the Part 1.

The Safety Analysis Set is the group of subjects who received at least 1 dose of the study drug.

The Pharmacokinetic Analysis Set is the group of subjects who received at least 1 dose of the study drug and whose at least 1 postdose sample of blood was taken for PK analysis.

The Efficacy Analysis Set is the group of subjects who received at least 1 dose of the study drug.

The PD and PGx Analysis Set is the group of subjects who received at least 1 dose of the study drug and had at least 1 PD and/or PGx data.

The number of subjects entered into Treatment Phase, the number and the percentage of subjects included in each analysis set will be presented. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized as defined in Section 5. Subject data listings will be provided.

5.2.2 Subject Disposition

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

Subject disposition table will include the number of subjects who were treated/not treated. Similarly, the number of subjects who discontinued the study treatment, and the primary reason for the study treatment discontinuation will also be summarized. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized as defined in Section 5.

Subject data listings will be provided.

5.2.3 Protocol Deviations

Important protocol deviation criteria will be established and subjects with important protocol deviations will be identified before the database lock. Also, all deviations related to COVID-19 will be identified.

Subject data listings will be provided.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in Safety Analysis Set. If the subjects included in PK Analysis Set is different from those who are in Safety Analysis Set, summarization on PK Analysis Set will be also performed in Part 1. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized as defined in Section 5.

Continuous demographic and baseline variables include

- Age
- Height
- Weight
- BMI
- Body surface area

Categorical demographic and baseline variables include

- Age group (< 65 years, ≥ 65 years)
- Sex
- Race
- Ethnicity
- ECOG-PS
- Smoking history

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

- Tumor type (for Part 1)
- Location of primary tumor (for Part 2)
- Tumor staging at diagnosis
- FGFR alternation (for UC cohort in Part 2)
- HPV (for SCCHN cohort in Part 2)
- PD-L1 status (for Part 2)
- Known gene mutation status (positive, negative)
- Biomarker status in tumor tissue (positive, negative)
  - CD31, α-SMA positive cancer associated fibroblast, acetylated α-tubulin in tumor tissue – if available
- Time from first diagnosis to the date of first study treatment (months) (as continuous variable)
- Involved disease organ
- Number of involved disease organ (1, 2, ≥3)

- Number of previous anticancer medication as regimen (1, 2, ≥3)
  - For Part 1, unique number of regimen number used for locally advanced or metastatic setting as recored in previous anti-cancer medication form are counted.
  - For Part 2, number of systemic therapy recorded in tumor diagnosis form are counted.
- Subjects with any previous anti-cancer surgery
- Subjects with any previous radiotherapy
- Subjects with any previous anti-cancer procedure other than surgery

Subject data listings will be provided.

Medical History

A subject data listing of medical history and current medical condition will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Prior medications will be defined as medications that started before the first dose of study treatment. Concomitant medications will be defined as medications that (1) started before the first dose of study treatment 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 treatment up to 30 days after the subject's last dose. Medications received after 30 days of last dose will be considered as post treatment medications.

The number (percentage) of subjects who took each prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class (anatomical class, pharmacological class), and WHO DD preferred term on the Safety Analysis Set. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized as defined in Section 5. For Part 2, the number (percentage) of subjects who received previous anti-cancer medication will be summarized in same manner.

Non-pharmacological procedures will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA).

All medications and non-pharmacological procedures will be presented in subject data listings.

5.2.6 Treatment Compliance

Subjects with treatment related important or COVID-19 related protocol deviations will be provided in the subject data listings.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

No adjustment for covariates will be performed.

5.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

5.3.4 Examination of Subgroups

The subgroup analyses will not be performed.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

The details of handling of missing data will be described in the section 8.

5.3.6 Other Considerations

Accelerated mTPI Design

An accelerated mTPI design will be employed to determine the MTD of E7130. When a drug-related Grade ≥2 toxicity is not observed in the first dose cohort (3 subjects) of every 2 weeks regimen, dose will be escalated in successive cohorts by single-subject DLT assessment until such a toxicity is observed. If such a toxicity is developed, the cohort will be expanded to evaluate DLT in 3 subjects and mTPI design with cohort size of 3 will be adopted.

The mTPI design uses a Bayesian statistical framework and a beta/binomial hierarchic model to compute the posterior probabilities of three intervals that reflect the relative distance between the DLT rates of each dose level to the target DLT rate of 25%.

Decision rules for dose-finding are based on calculating the unit probability mass (UPM) of three intervals corresponding to 0 to <20% (underdosing), 20 to 30% (proper dosing) and >30 to 100% (overdosing) in terms of toxicity. The UPM for each interval is defined as the probability of the interval divided by the length of the interval, and the one with the largest UPM implies the decision for future dose level to be assigned, i.e., 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 precalculated and presented.

Determination of MTD

MTD will be determined when the lowest dose has a >95% posterior probability of being DLT rate >25% (i.e., unacceptable DLT rate beyond the target DLT rate) or a prespecified maximum sample size, 7 or 5 cohorts being composed of 3 subjects in every 2 weeks or every 3 weeks regimen respectively (except for initial dosing cohort in biweekly regimen), is reached. However, the maximum sample size will be adjusted as necessary according to the actual number of dose levels that will be evaluated and the number of subjects evaluable for DLT. In addition, if the Bayesian predictive probability that future dose assignments will be S is 80% or greater (in other words, if it is considered highly likely that future registered subjects will also be assigned to the current dose level) when 9 further subjects are added to a particular dose level, subject registration will be closed early and the MTD can be determined.

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 ≤95% posterior probability of being DLT rate >25%. Toxicity data until Cycle 2 is taken into account to finally determine MTD. 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, D, 1983) will be used to maintain monotonically increase of DLT rate with increasing dose level.

5.4 Efficacy Analyses

Efficacy analyses will be conducted based on the Efficacy Analysis Set. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized as defined in Section 5.

5.4.1 Primary Efficacy Analyses

Since this trial is phase 1, primary efficacy endpoint is not defined.

Part 1

Based on the tumor assessments according to RECIST v1.1, BOR will be summarized. If a subject had a best overall response of non-CR/non-PD, the subject's best overall response will be grouped with the SD category. ORR, DCR, CBR and its corresponding exact 2-sided 95% confidence intervals will be calculated.

A waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir (ie, maximum tumor shrinkage). A spider plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions.

Part 2

Besides the similar analyses for the Part 1, followings will be summarized.

PFS is defined as the time from the date of first dose to the date of first documented PD or death due to any cause (whichever occurs first) and calculated as below. For subjects who did not have an event, PFS will be censored. Censoring rules for PFS are shown in Table 2.

Note: Tumor assessment results after censoring or event of PFS will NOT be used in any efficacy summaries based on tumor assessment. For Part 1, PFS is not evaluated but same rule should be applied. Subject data listing contains all tumor assessment results.

PFS (months) = (Date of first documented PD/ death/ censored date – Date of first dose + 1) / (365.25/12).

The cumulative PFS rate will be calculated using Kaplan-Meier method. The median, Q1, and Q3 for PFS with their 95% CIs will be evaluated. The 95% CIs will be calculated based on Greenwood formula and log-log transformation. The number (percentage) of subjects with event/censored will be summarized. The PFS rate with its 95% CI at appropriate timepoints (e.g. 2, 4, 6 months) will also be calculated. Kaplan-Meier plots with the number of subjects at risk will be presented.

DOR is defined as the time from the date of first documented date of CR or PR to the first documented date of event (disease progression or death from any cause, whichever occurs first). Censoring rules for DOR is same as PFS.

DOR (months) = (Date of first documented PD/ death/ censored date – Date of first documented CR or PR + 1) / (365.25/12).

For subjects whose BOR is PR or CR, DOR will be summarized in same manner as with PFS.

OS is defined as the time from the date of first study dose to the date of death from any cause and calculated as below. Subjects who were lost to follow-up or the subjects who were alive at the date of data cutoff will be censored at the date the subject was last known alive or the cut-off date, whichever comes earlier. Censoring rules for OS are shown in Table 3. OS will also be summarized in the same manner as with PFS. In addition, duration of survial follow-up time will also be summarized by median, Q1, and Q3 with their 95% CIs. Survival follow-up time is calculated in the same way as the Kaplan-Meier estimate of overall survival but the indicator of "censor" and "event" is reversed.

OS (months) = (Date of death/ censored date – Date of first dose + 1) / (365.25/12).

TTR is defined as the time from the date of first dose to the date of first documented date of CR or PR. For subjects whose BOR is PR or CR, TTR will be summarized using summary staitistics as continuous variable.

TTR (months) = (Date of first documented CR or PR – Date of first dose + 1) / (365.25/12).

A swimmer plot will be presented for the duration of treatment in each subject. A waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir (ie, maximum tumor shrinkage). Also, duration of treatment of each subject and maximum tumor shrinkage will be presented in one figure.

Subject data listings will be provided.

Table 2 Censoring rules for PFS

No.	Situation	Date of Event or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
3	No progression nor death at the time of data cut-off	Date of last adequate radiologic assessment* prior to or on date of data cut-off	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment* prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Event
6	Death between adequate assessment visits*	Date of death	Event
7	Death or progression after two or more consecutive missed visit/tumor assessment**	Date of last adequate radiologic assessment* before missed tumor assessments	Censored

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** Two or more missed visit is defined if the duration between the last adequate tumor assessment and death or PD is longer than 182 days (ie. 12 weeks x 2 + 2 weeks [allowance of tumor assessment]) considering the subjects on the every 12-week scanning schedule in this study after Week 24.

The priority of the censoring rules is as follows:
1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of first dose. However, if the subject died within 175 days (25 weeks) after the first dosing date and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
- If a subject had new anticancer treatment before PD or death (No. 4), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more assessments consecutively before PD or death (No. 7), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criteria, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, 5, 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, 3, 4, 7).

Table 3 Censoring rules for OS

No.	Situation	Date of Event or Censoring	Outcome
1	Death before or on data cut off	Date of Death	Event
2	Death after data cut off	Date of data cut off	Censored
3	Subject still alive at data cut off	Date of data cut off	Censored
4	Subject lost to follow-up or withdraw of consent before data cut off	Date last known to be alive	Censored
5	Alive before data cut-off but survival status is unknown at data cut-off	Date last known to be alive	Censored

5.4.2 Secondary Efficacy Analyses

Not applicable.

5.4.3 Other Efficacy Analyses

For evaluated tumor marker parameters, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using summary statistics. Spaghetti plot will be also presented for each subject. The percent change from baseline will also be used if deemed necessary.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual listings of E7130 plasma and urinary concentrations and PK parameters.

The PK Analysis Set will be used for the summaries of E7130 plasma and urinary concentrations and PK parameters.

In Part 1 of this study, using non-compartmental analysis, plasma concentrations of E7130 will be analyzed to determine the PK parameters including C_{max}, t_{max}, AUC, $t_{½}$, CL, and V_d. Urinary concentrations of E7130 will be analyzed to determine the PK parameters including amount of unchanged drug excreted in urine in subjects who have urine samples in Part 1, if possible. Plasma concentration data in Part 2 of this study will be used to population PK analysis integrating plasma concentration data from Part 1 and other future studies. For population PK analysis, the details will be described in the separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

The data in patient with dose interruption during IV infusion or patient who has no completion of study drug administration will not be used for pharmacokinetic analyses at the relevant visit. The data in patient with dose skip, dose delay, or dose reduction will not be included on calculation of summary statistics.

For summary statistics, following infusion time category will be used; 5 min = 0 min to less than 7.5 min, 10 min = 7.5 min to less than 12.5 min, 15 min = 12.5 min to less than 22.5 min, 30 min = 22.5 min to less than 45 min, 60 min = 45 min to less than 90 min, 120 min = 90 min over.

5.5.1.1 Plasma Concentrations and its PK Parameter Analysis

<Plasma Concentration>

In Part 1, plasma concentrations of E7130 will be summarized using summary statistics (n, mean, SD, median, minimum and maximum) by each dose group and infusion time separately by regimen (every 2 weeks/every 3 weeks) and nominal time points. Plasma concentrations of E7130 will be listed for each subject by each dose group and infusion time separately by regimen, and actual sampling time.

In Part 2, plasma concentrations of E7130 will be listed for each subject by each dose group and infusion time separately by regimen, and actual sampling time.

<Plasma PK Parameter>

PK parameters will be derived by noncompartmental analysis using Phoenix WinNonlin software (version 6.2.1 or later) according to Eisai non-compartmental pharmacokinetic Analysis Manual (302-104.01-MNL).

Plasma concentrations of E7130 at predose on next dosing will be used for calculation of individual PK parameters after Cycle 1 Day 1 and Cycle 2 Day 1 (eg, E7130 concentration data at predose on Cycle 1 Day 15 will be used for calculation of plasma PK parameters after Cycle 1 Day 1 dosing in every 2 weeks regimen).

The following PK parameters for E7130 will be calculated in Part 1:

Cycle 1 Day1 and Cycle 2 Day 1

C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $t_{½}$, MRT, λ_z, CL, V_{ss}

The following PK parameters will be calculated on Cycle 1 Day 1 only:

For every 2 weeks regimen; $AUC_{(0-168h)}$, $AUC_{(0-336h)}$, AUC ratio (RAAUC1) [RAAUC1 will be obtained as $RAAUC1=[(AUC_{(0-336h)}- AUC_{(0-168h)})/AUC_{(0-inf)}]*100$], AUC ratio (RAAUC3) [RAAUC3 will be obtained as $RAAUC3=[1-(AUC_{(0-336h)}/AUC_{(0-inf)})]*100$]

For every 3 weeks regimen; $AUC_{(0-336h)}$, $AUC_{(0-504h)}$, AUC ratio (RAAUC2) [RAAUC2 will be obtained as $RAAUC2=[(AUC_{(0-504h)}- AUC_{(0-336h)})/ AUC_{(0-inf)}]*100$], AUC ratio (RAAUC3) [RAAUC3 will be obtained as $RAAUC3=[1-(AUC_{(0-504h)}/AUC_{(0-inf)})]*100$]

The following PK parameters will be calculated on Cycle 2 Day 1 only:

$AUC_{(0-t)}$, $R_{ac}(C_{max})$, $R_{ac}(AUC)$, R_{ss}

Cycle 1 Day 15, Cycle 2 Day 15 (every 2 weeks regimen only)

C_{max}, t_{max}

Other PK parameters may be calculated as appropriate. For each dose group and infusion time separately by regimen, summary statistics will be tabulated for the PK parameters. Summary statistics (n, mean, SD, median, minimum and maximum) will be presented for all parameters (apart from t_{max} where mean and SD are not required). In addition, geometric mean and %CV will also be presented for all parameters apart from t_{max}.

PK parameters of E7130 for each subject will be listed.

5.5.1.2 Urine Concentration and its PK Parameter Analysis

Urine volume and urinary concentrations of E7130 will be listed for each subject by each dose group, infusion time, collection period separately by regimen and actual sampling time in Part 1.

The following urinary PK parameters will be derived by SAS and/or Phoenix WinNonlin according to 302-104.01-MNL.

Cycle 1 Day 1

<Urinary PK parameter>

Amount of E7130 recovered in urine ($A_{e(t1\text{-}t2)}$) by each collection interval

Cumulative amount of $A_{e(t1\text{-}t2)}$ in urine until end of each collection interval ($A_{e(0\text{-}x)}$) and total collection period ($A_{e(0\text{-}t)}$)

Fraction of dose excreted (Fe; % of dose) in urine by each collection interval

Cumulative Fe in urine until end of each collection interval and total collection period

Summary statistics (n, mean, SD, median, minimum and maximum) will be tabulated for the urinary PK parameters of E7130 respectively by each dose group, infusion time and collection period.

Urinary PK parameters of E7130 for each subject will be listed.

5.5.1.3 Pharmacokinetic Data Figures

<Plasma Concentration>

The following figures will be displayed separately by regimen in Part 1.

Linear and semi-log plots of mean E7130 plasma concentration-time profiles of all dose groups separated by infusion time will be displayed in the same graph using nominal time with SD by Cycle (Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing) up to 168 hours and 336 hours after the end of infusion respectively for every 2 weeks regimen and every 3 weeks regimen.

Linear plots of mean E7130 plasma concentration-time profiles of all dose groups separated by infusion time will be displayed in the same graph using nominal time with SD by Cycle (Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing) up to 4 hours after the end of infusion.

Linear and semi-log plots of mean E7130 plasma concentration-time profiles after Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing will be displayed using nominal time by each dose group separated by infusion time in the same graph up to 168 hours and 336 hours after the end of infusion respectively for every 2 weeks regimen and every 3 weeks regimen.

Linear plots of mean E7130 plasma concentration-time profiles after Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing will be displayed using nominal time by each dose group separated by infusion time in the same graph up to 4 hours after the end of infusion.

Linear and semi-log plots of E7130 plasma concentration-time profiles of all subjects by each dose group separated by infusion time will be displayed using actual time by Cycle (Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing) up to 168 hours and 336 hours after the end of infusion

respectively for every 2 weeks regimen and every 3 weeks regimen.

Linear and semi-log plots of E7130 plasma concentration-time profiles after all doses will be displayed using actual time by individual subject up to 168 hours and 336 hours after the end of infusion respectively for every 2 weeks regimen and every 3 weeks regimen.

Linear plots of E7130 plasma concentration-time profiles after all doses will be displayed using actual time by individual subject up to 4 hours after the end of infusion.

Linear and semi-log plots of E7130 plasma concentration-time profiles after Cycle 1 Day 1 and Cycle 2 Day 1 dosing will be displayed using actual time by individual subject. Plasma concentrations of E7130 at predose on next dosing will be used for E7130 plasma concentration-time profiles after Cycle 1 Day 1 and Cycle 2 Day 1 (eg, E7130 concentration data at predose on Cycle 1 Day 15 will be used for plots after Cycle 1 Day 1 dosing in every 2 weeks regimen).

5.5.1.4 Evaluation of Dose-Proportionality in PK Parameters

The PK Analysis set will be used for evaluation of dose proportionality. This will be applicable where there are PK parameters of at least 3 dose levels separately by regimen. The dose proportionality for E7130 will be investigated using PK parameters obtained from non-compartmental analysis after Cycle 1 Day 1 dosing in Part 1. Proportionality of C_{max} will be evaluated only in patients with infusion time category of 1 hour ie, actual infusion time of 45 min to less than 90 min.

Doses ($\mu g/m^2$) will be plotted on the X axis and each parameter (C_{max} and $AUC_{(0\text{-}inf)}$ for both regimen, $AUC_{(0\text{-}336h)}$ for every 2 weeks regimen, and $AUC_{(0\text{-}504h)}$ for every 3 weeks regimen) will be plotted on the Y axis to display the data of all subjects.

PK parameter (C_{max} and $AUC_{(0\text{-}inf)}$ for both regimen, $AUC_{(0\text{-}336h)}$ for every 2 weeks regimen, and $AUC_{(0\text{-}504h)}$ for every 3 weeks regimen) will be employed in assessing dose proportionality using the power model, assuming $C_{max} = \alpha\ (dose)^{\beta}$, which is equivalent to the logarithm transformation model:

$\log (C_{max}) = \log (\alpha) + \beta \log(dose)$

The linear regression model will be used to assess the slope parameter (β) and estimate the 95% confidence intervals for β.

The same analysis will be performed for $AUC_{(0\text{-}inf)}$ for both regimen, $AUC_{(0\text{-}336h)}$ for every 2 weeks regimen, and $AUC_{(0\text{-}504h)}$ for every 3 weeks regimen.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The PD and PGx Analysis Set will be used for biomarker analysis in blood samples and the analysis will be conducted in Part 2 on each UC and SCCHN subject group. Dose levels of each cancer will be pooled for summarization. For selected markers, box plot will be displayed for actual value at baseline to early postbaseline visit. Percent change from baseline will also be presented in same manner. For collagen IV, preclinical data showed

E7130 increases plasma collagen IV with different time points in a tumor model dependent manner. Based on this finding, largest value and largest percent change from baseline by Cycle 2 Day 1 of collagen IV will be displayed by box plot with baseline value. Also, actial value at baseline and early postbaseline visits will be plotted for selected markers of each subject (i.e. spaghetti plot).

For selected markers in Part 2 subjects, percent change from baseline at each postbaseline will be summarized with median. Each post-baseline percent change from baseline will be tested by one-sample Willcoxon test and its P-value will be presented. Using the P-value, Q-value to investigate false discovery rate for each marker at a timepoint will also be presented.

Subject data listings will be provided.

5.5.3 Pharmacokinetic / Pharmacodynamic Analyses

E7130 concentration-QTc analysis will not be conducted.

5.6 Safety Analyses

DLT analyses will be performed on the DLT Analysis Set by each dose group and for total dose groups. The Safety Analysis Set will be used for all other safety analyses. The safety analysis will be performed by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized as defined in Section 5. Safety data will be summarized on an "as treated" basis using summary statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; number [percentage] for categorical variables).

5.6.1 Extent of Exposure

For every 2 weeks regimen, the parameters to be summarized are defined as follows.

- Number of cycles = The last cycle with study drug dosing
- Duration of treatment (days) = Date of Day 1 of the last cycle with study drug dosing + 28 – first dosing date
- Duration of treatment (months) = (Date of Day 1 of the last cycle with study drug dosing + 28 – first dosing date) / (365.25/12)
- Number of subject-month with study drug dosing = Sum of duration of treatment (months) per subjects
- Total doses ($\mu g/m^2$) = Sum of all the actual dose derived by;
  (Planned dose of each cycle [$\mu g/m^2$]) x (Actual volume infused [ml] / volume to be infused [ml])
- Dose intensity ($\mu g/m^2$/4 weeks) = Total doses / (Duration of treatment [days] / 28)
- Relative dose intensity (%) = 100 × Dose intensity / Planned total dose in Cycle 1 ($\mu g/m^2$)

For every 3 weeks regimen, the parameters to be summarized are defined as follows.

- Number of cycles = The last cycle with study drug dosing
- Duration of treatment (days) = Date of Day 1 of the last cycle with study drug dosing + 21 – first dosing date
- Duration of treatment (months) = (Date of Day 1 of the last cycle with study drug dosing + 21 – first dosing date) / (365.25/12)
- Number of subject-month with study drug dosing = Sum of duration of treatment (months) per subjects
- Total doses ($\mu g/m^2$) = Sum of all the actual dose derived by;
  (Planned dose of each cycle [$\mu g/m^2$]) x (Actual volume infused [ml] / volume to be infused [ml])
- Dose intensity ($\mu g/m^2$/3 weeks) = Total doses / (Duration of treatment [days] / 21)

- Relative dose intensity (%) = 100 × Dose intensity / Planned total dose in Cycle 1 ($\mu g/m^2$)

The number (percentage) of subjects who experienced dose skip (ie. no drug administration on scheduled date), dose delay (ie. postponing the next dosing), dose reduction, dose interruption (ie. permanent or temporary administration stopping during a certain drug infusion) will be provided. When "Planned Dose" is 0 and "Study drug start date" is completed, they are considered as dose skip event. For every 2 weeks regimen, the following two cases are considered as dose delay event; 1) Cycle X Day 15 - Cycle X Day 1 >= 16 days, 2) Cycle X + 1 Day 1 - Cycle X Day 15 >= 21 days. For every 3 weeks regimen in Part 1, when Cycle X + 1 Day 1 - Cycle X Day 1 >= 28 days, it is considered as dose delay event. For every 3 weeks regimen in Part 2, the following two cases are considered as dose delay event; 1) Cycle 2 Day 1 – Cycle 1 Day 1 >= 22 days, 2) Cycle X + 1 Day 1 – Cycle X Day 1 >= 24 days (X >= 2). When a planned dose is less than previous one but more than 0, it is considered as dose reduction event. When "Study Drug Interruption" in Study Medication form of CRF is checked OR doses of actual volume infused is less than volume to be infused, it is considered as dose interruption event.

In addition, cycle of first dose reduction (2, 3, 4, 5, >=6) and frequency of dose reduction (0, 1, 2, >=3) is summarized.

Subject data listings will be provided.

5.6.2 Adverse Events

DLTs (Part 1 only)

The number (percentage) of subjects who experienced DLT will be summarized. DLT will also be summarized by below criteria as reported in CRF.

- Febrile neutropenia
- Grade4 neutropenia that persists for more than 7 days or any neutropenia that requires hematopoetic stimulating agents.
- Grade 4 thrombocytopenia, or thrombocytopenia that requires platelet transfusion
- Grade 4 anemia, or anemia that requires blood transfusion.
- Any Grade 3 or higher non-hematological toxicity with the exception of abnormal clinical laboratory values with no clinical significance, or any events which can be managed and controlled to Grade 2 or less by maximal medical management
- Any Grade 4 non-hematological toxicity
- In every 2 weeks regimen, development of any toxicity that is considered to be related to E7130 and where dose skip at C1D15 is necessary.

- In every 3 weeks regimen, development of any toxicity that is considered to be related to E7130 and where dose at C2D1 is necessary to postpone for over 14 days for recovery from the toxicities

The estimates of DLT rate based on Bayesian statistics will be provided using non-informative beta prior distribution of Beta (0.005, 0.005) by each dose. The estimates will include posterior mean, median, mode (if applicable), variance, standard deviation, 95% highest posterior density (HPD) credible interval, probability of > 25%, 0 - 20%, 20 - 30% and 30 - 100%. If the posterior mean does not increase monotonically, adjusted posterior mean using the PAVA, weighted by inverse of posterior variance in each dose level, will also be shown.

All DLTs will be presented in subject data listings.

Adverse events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the MedDRA. Adverse events will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE), defined in the section 8.3, will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

An overview table, including the incidence of and the number of subjects with TEAEs, Treatment-related TEAEs, TEAEs with grade 3 or above, serious adverse events (SAEs), deaths, and TEAEs that led to discontinuation, dose reduction and, dose interruption of study treatment will be provided based on the report in AE form of CRF.

The incidence of below events will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT.

- TEAEs
- TEAEs with frequency >= 10%
- TEAEs by the highest CTCAE grade
- TEAEs grade 3 or above
- Serious TEAEs
- Non-serious TEAEs
- Treatment-related TEAEs

- Treatment-related TEAEs with frequency >= 10%
- Treatment-related TEAEs by the highest CTCAE grade
- Treatment-related TEAEs grade 3 or above
- Treatment-related serious TEAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to dose reduction of study treatment
- TEAEs leading to dose interruption of study treatment
- COVID-19 related TEAEs

All deaths within 30 days of last dose and deaths >30 days of last dose will also be summarized. The AEs leading to death will also be summarized by its reason (due to disease progression, not due to disease progression) from AE form of CRF in same table.

Subject data listings of all deaths, SAEs, AEs leading to death, discontinuation of study treatment, dose reduction of study treatment, dose interruption of study treatment and all AEs will be provided.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using summary statistics. Qualitative parameters will be summarized by number and percentage of subjects, and changes from baseline to each postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Box plot display will be used to show the longitudinal change of actual data of the parameters by visit.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value is below (L), within (N), or above (H) the laboratory parameter`s reference range. The result of LNH classification will be provided in a subject data listing.

Laboratory parameters will be graded by CTCAE ver. 4.03 in the section 13.1. Changes from CTCAE grade at baseline to each postbaseline visit and worst postbaseline will be reported using shift tables. CTCAE will also be used to identify subjects with Treatment-emergent markedly abnormal laboratory value (TEMAV). The number (percentage) of subjects with TEMAV (markedly abnormal high/low) will be summarized for each visit and overall study period. The changes from baseline to each postbaseline visit and overall study period will also be reported using shift tables. The TEMAV will be defined in the section 8.3.

Subject data listing will be provided.

5.6.4 Vital Signs

Summary statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature), weight, and SpO_2 and changes from baseline will be presented by visit.

Box plot display will be used to show the longitudinal change of actual data of the parameters by visit.

Subject data listings will be provided.

5.6.5 Electrocardiograms

ECG evaluation by clinical site

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each visit.

Subject data listings will be provided.

ECG evaluation by central reviewer

Summary statistics for ECG parameters (Heart Rate, RR, PR, QRS, QT, and QTcF) and changes from baseline will be presented by time point. For Part 1, the results assessed at same time points (ie. before dose, 10 minutes after end of infusion, 2 hours after end of infusion, 4 hours after end of infusion) in baseline assessment will be used as the baseline data and change from baseline will be calculated. For timepoint of 24 hours after dose, result of before dose in baseline assessment will be used as baseline. As for Part 2, baseline data is defined as the last non-missing value observed prior to the first dose of study treatment. If the relevant baseline data is missing, the change from baseline will also be calculated as missing. For continuous variable in Part 2, mean of 3 timepoints before first study treatment is used as baseline value. When one or two value(s) of the 3 timepoints is/are missing, non-missing values are used for calculation of the mean.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not evaluable) to each visit. For ECG interpretation, worst result of each timepoint is selected for the representative value (abnormal > normal > not evaluable).

In addition, the number (percentage) of subjects who met below criteria at least one postdose abnormal ECG result in QTcF measured at the external ECG assessment organization will be presented:

Absolute QTcF interval prolongation:

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

- QTcF interval >500 ms

Change from baseline in QTcF interval:

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

Subject data listings will be provided.

5.6.6 Other Safety Analyses

ECOG PS

The number (percentage) of subjects for each category of ECOG PS will be summarized by visit. The highest postbaseline scale of ECOG PS for each subject will also be summarized.

Subject data listings will be provided.

Potential Hy's law cases

A subject data listing for potential subjects who meet Hy's law criteria will be presented. Potential subjects meeting Hy's law criteria are those who meets following definition at a same timepoint including baseline and postbaseline:

Elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal

AND

Elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal

AND

Alkaline phosphatase lab value that is less than 2X the upper limit of normal.

5.7 Other Analyses

No other analysis is planned for this study.

5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

6 INTERIM ANALYSES

There is no formal interim analysis planned. DLT assessment will be on an ongoing basis according to the dose escalation schedule. Analyses may be performed for each cohort in Part 2 separately.

In urothelial carcinoma cohort of part 2, interim evaluation will be performed to determine whether sample size is increased or not. If BOR of CR or PR is observed in 2 subjects or more out of 10 subjects in one initial dose level (i.e. 410 μg/m^2 Q3W, or lower initial dose level when applicable) of cohort 2, additional 20 subjects will be enrolled in the dose level. CR and PR must be confirmed by another scan in 4 weeks or later from the first observation.

The detail of criteria to increase sample size in cohort 2 of Part 2 is following. Prior Beta (1,1) will be used in posterior probability estimation. After tumor assessment in 10 subjects received a dose level in UC cohort have been followed for sufficient time, a futility evaluation will be done using posterior probability with a probability cutoff of 60% and a threshold objective response rate (ORR) of 20% for UC. Number of subjects in UC cohort with the dose level will be expanded if the posterior probability of ORR >20% is at least 60% to a total of 30 (10 subjects from expansion cohort, 20 subjects from additional expansion cohort); i.e. there are 2 or more responders among the first 10 subjects, the cohort will be expanded. The cohort will not be expanded if the posterior probability of ORR >20% is less than 60%.

7 CHANGES IN THE PLANNED ANALYSES

A summary of all major additions, changes and deletions in the planned analyses described in the protocol will be provided in this section.

- The definition of prior medication (non-anticancer medication) was updated to align with new standard.
- Summary group in Part 2 was reconsidered and defined.
- Waterfall and spaghetti plot will be generated in Part 1 also.
- CCI [redacted]
- Time to response will be summarized.

Pharmacokinetic Analyses

- Because it was decided not to collect urinary and fecal samples between 0-168 hour in Part 1 for pharmacokinetic analysis (protocol ver 06), related descriptions in this document were deleted.

Plasma E7130 concentration-QTc analysis Analyses

- Plasma E7130 concentration-QTc analysis will not be conducted.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

8.1 General Data Handling

Definition of Baseline data

Except for electrocardiograms assessment in Part 1, baseline is defined as the last non-missing value observed prior to the first dose of study treatment for a given parameter.

The definition of baseline data for electrocardiograms in part 1 is shown in Section 5.6.5.

Definition of Change from Baseline, Percent Change from Baseline

Change from baseline is defined as post-baseline value minus baseline value.
Percent change from baseline is defined as follows:

% Change from baseline = (Change from baseline / Baseline) * 100%

For any Baseline value of 0, the subject's corresponding percent change from baseline will not be included in the summary statistics table.

Calculation of Body Surface Area

Du Bois method will be used to calculate body surface area (BSA).

BSA (m^2) = $height^{0.725}$ (cm) * $weight^{0.425}$ (kg) * 0.007184

8.2 Efficacy Data Handling

Handling of missing data for tumor assessment result

For the calculation of ORR, DCR and CBR, subjects with missing response status (subjects whose baseline is missing and/or no adequate post-baseline tumor assessments result) will be not included in numerator, but included in denominator.

8.3 Safety Data Handling

Treatment-emergent adverse event

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during the time from the first dose of study drug to 30 days following the last dose of study drug, having been absent at pretreatment (Baseline) or

- Reemerged during treatment, having been present at pretreatment but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

Adverse Events

Adverse Events with incomplete start dates will be considered treatment emergent 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;

d. Year is missing;

e. Complete date is missing.

Concomitant Medications

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;

e. Complete date is missing.

TEMAV (Treatment-Emergent Markedly Abnormal Value)

Treatment-emergent markedly abnormal laboratory value (TEMAV) is defined as a postbaseline laboratory value with grade 3 or higher, and with a grade increase from baseline.

(ie., Increasing grade 0 to 3 or higher, grade 1 to 3 or higher, grade 2 to 3 or higher, grade 3 to 4 or 5, grade 4 to 5.)

Handling of below lower quantification values in laboratory results

In the cases where laboratory result contains below lower quantification (BLQ) value, it will be replaced to the lower limit value of quantification (LLOQ) for summary tables.

Visit Windows

The analysis window for safety analysis is based on the visits recorded in CRF. In the calculation of descriptive statistics for safety parameters (e.g, laboratory values and vital signs, etc.) per scheduled visit, and change from baseline per visit, if multiple observations are recorded in one scheduled visit, the earliest record will be used for summary tables. Other safety analyses (e.g, worst grade laboratory results, individual plotting) will include all observations.

8.4 Pharmacokinetic Data Handling

8.4.1 Lower Limit of Quantification of E7130 Plasma Concentration

The LLOQ of E7130 concentration in plasma and urine are 0.00200 ng/mL, and 0.100 ng/mL, respectively.

8.4.2 BLQ Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, BLQ values will be handled according to 302-104.01-MNL.

8.4.3 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.01-MNL.

8.4.4 BLQ Handling for Developing Figures of individual ECG parameter values – plasma Concentration of E7130

When developing figures of individual ECG parameter (QTcF or ΔQTcF) values-plasma concentration of E7130, BLQ values will be assigned to "zero".

8.4.5 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow 302-104.01-MNL.

8.4.6 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD and CV) will have 3 significant digits. For t_{max}, raw values are median are shown in fixed 2 decimal places.

Typical variable	Unit	N	Digit rule	Raw Minimum Maximum	Mean Median	SD	Geometric Mean	CV (%)
Plasma E7130 concentration	ng/mL	X	Significant digits	3	3	3	-	-
Urinary E7130 concentration	ng/mL	X	Significant digits	3	3	3	-	-
C_{max}	ng/mL	X	Significant digits	3	3	3	3	3
t_{max} [a]	h	X	Fixed decimal places	2	2	-	-	-

λ_z	1/h	X	Significant digits	3	3	3	3	3
$t_{1/2}$	h	X	Significant digits	3	3	3	3	3
$AUC_{(0-t)}$ $AUC_{(0-tb)}$ $AUC_{(0-inf)}$	ng•h/mL	X	Significant digits	3	3	3	3	3
$\%AUC_{ex}$	%	X	Significant digits	3	-	-	-	-
CL	L/h/m^2	X	Significant digits	3	3	3	3	3
V_{ss}	L/m^2	X	Significant digits	3	3	3	3	3
MRT	h	X	Significant digits	3	3	3	3	3
A_e	µg	X	Significant digits	3	3	3	3	3
Fe	%	X	Significant digits	3	3	3	3	3
R_{ac}, R_{ss}		X	Significant digits	3	3	3	3	3
RAAUC	%	X	Significant digits	3	3	3	3	3

a: Mean, SD, geometric mean and CV will not be calculated for t_{max}.

CV(%)= sqrt(exp[SD^2 of log transformed data]-1)×100

NOTE: The following parameters are reported in the CSR, but appear in Listings only. They are important information to confirm that individual $t_{1/2}$ and its related parameters such as $AUC_{(0-inf)}$ are appropriately derived and allow those PK parameters to be reproduced when necessary.

a) Time points used for estimation of λ_z (lower and upper)
b) Number of the time points used for λ_z
c) Adjusted regression coefficient (R^2adj)
d) Percentage of $AUC_{(0-inf)}$ obtained by extrapolation ($\%AUC_{ex}$)
e) The last time points used for calculation of $AUC_{(0-t)}$ (t_{last})
f) The interval of the terminal disposition phase duration expressed as the number of half lives (λ_z Span)

In Listings, a) and e) are shown in same digits as actual sampling time after dosing used for calculation of PK parameters. For b), integer number is used in Listings. For c), d), and f), significant 3 digits are used in Listings.

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS (version 9.3 or later) or WinNonlin (Professional version 6.2.1 or later). As necessary, other validated statistical software will also be used.

Validation method and analysis conductor

All statistical analyses apart from PK parameter calculation will be conducted by a contract research organization, using validated standard programs or double programming. For analyses needed in data review, single programming will be used. PK parameter calculation will be conducted by Eisai.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

- Bartholomew, D. Isotonic inference. In: Samuel K, Norman LJ, editors. Encyclopedia of Statistical Science volume 4, New York: Wiley-Interscience. 1983;260-5.
- Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7:653-63.
- Ji Y, Wang, S. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3 + 3 Design for Practical Phase I Trials. J Clin Oncol. 2013;31:1785-91.
- FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Dec 2018 [internet; cited on 1st Aug 2024] Available from: https://www.fda.gov/media/71195/download.

13 APPENDICES

13.1 National Institute for Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

National Cancer Institute (NCI) Cancer therapy evaluation program Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 May 2009 (v4.03 June 2010) is available online at:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

CTCAE grades for selected laboratory parameters are listed in the table below, where ULN is the upper limit of normal and LLN is the lower limit of normal.

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology					
Hemoglobin (low)	100 - <LLN (g/L)	80 - <100 (g/L)	<80 (g/L)	__	Death
Hemoglobin (high)	Increase in >0 - 20 g/L above ULN (ie., Increase in >0 - 2 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >20 - 40 g/L above ULN (ie., Increase in >2 - 4 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >40 g/L above ULN (ie., Increase in >4 gm/dL above ULN) or above baseline if baseline is above ULN	—	—
Platelet Count (PLT) (low)	75 - <LLN (x 10^9/L)	50 - <75 (x 10^9/L)	25 - <50 (x 10^9/L)	<25 (x 10^9/L)	—
White Blood Cell Count (WBC) (low)	3 - <LLN (x 10^9/L)	2 - <3 (x 10^9/L)	1 - <2 (x 10^9/L)	<1 (x 10^9/L)	—
White Blood Cell Count (WBC) (high)	—	—	>100 x 10^9/L (ie., >100,000/mm^3)	—	Death
Lymphocytes (low)	0.8 - <LLN (x 10^9/L)	0.5 - <0.8 (x 10^9/L)	0.2 - <0.5 (x 10^9/L)	<0.2 (x 10^9/L)	—
Lymphocytes (high)	—	>4 - 20 (x 10^9/L) (ie., >4,000 - 20,000/mm^3)	>20 (x 10^9/L) (ie., > 20,000/mm^3)	—	—
Neutrophils (low)	1.5 - <LLN (x 10^9/L)	1 - <1.5 (x 10^9/L)	0.5 - <1 (x 10^9/L)	<0.5 (x 10^9/L)	—

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood Coagulation					
INR (high)	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	—	—
Blood Chemistry					
Albumin (low)	30 - <LLN (g/L)	20 - <30 (g/L)	<20 (g/L)	—	Death
Alkaline Phosphatase (ALP) (high)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	—
ALT (SGPT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	—
Amylase (high)	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	
AST (SGOT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	—
Total Bilirubin (high)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	—
Calcium, serum-low (hypocalcemia)	2.0 - <LLN (mmol/L) (ie., 8.0 mg/dL - <LLN) *	1.75 - <2 (mmol/L) (ie., 7.0 - <8.0 mg/dL) *	1.5 - <1.75 (mmol/L) (ie., 6.0 - <7.0 mg/dL) *	<1.5 (mmol/L) (ie., <6.0 mg/dL) *	Death
Calcium, serum-high (hypercalcemia)	>ULN – 2.9 (mmol/L) (ie., >ULN – 11.5 mg/dL) *	>2.9 – 3.1 (mmol/L) (ie., >11.5 – 12.5 mg/dL) *	>3.1 – 3.4 (mmol/L) (ie., >12.5 – 13.5 mg/dL) *	>3.4 (mmol/L) (ie., >13.5 mg/dL) *	Death
Cholesterol (high)	>ULN -7.75 mmol/L	>7.75 -10.34 mmol/L	>10.34 -12.92 mmol/L	>12.92 mmol/L	—
CPK (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	—
Creatinine (high)	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN	>6.0 x ULN	—
GGT (gamma-glutamyltransferase) (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5.0 x ULN	>5.0 x ULN – 20.0 x ULN	>20.0 x ULN	—
Glucose, serum-low (hypoglycemia)	3 - <LLN (mmol/L)	2.2 - <3 (mmol/L)	1.7 - <2.2 (mmol/L)	<1.7 (mmol/L)	Death

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Glucose, serum-high (hyperglycemia)	ULN – 8.9 (mmol/L)	>8.9 – 13.9 (mmol/L)	>13.9 – 27.8 (mmol/L)	>27.8 (mmol/L)	Death
Lipase (high)	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	—
Magnesium (low)	<LLN – 0.5 (mmol/L)	<0.5 – 0.4 (mmol/L)	<0.4 – 0.3 (mmol/L)	<0.3 (mmol/L)	Death
Magnesium (high)	>ULN – 1.23 (mmol/L)	—	>1.23 – 3.30 (mmol/L)	>3.30 (mmol/L)	Death
Triglyceride (hypertriglyceridemia) (high)	1.71 – 3.42 (mmol/L)	>3.42 – 5.7 (mmol/L)	>5.7 – 11.4 (mmol/L)	>11.4 (mmol/L)	Death
Phosphate, serum-low (hypophosphatemia)	0.8 - <LLN (mmol/L)	0.6 - <0.8 (mmol/L)	0.3 - <0.6 (mmol/L)	<0.3 (mmol/L)	Death
Potassium, serum-low (hypokalemia)	3.0 - <LLN (mmol/L)	—	2.5 - <3.0 (mmol/L)	<2.5 (mmol/L)	Death
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 (mmol/L)	>5.5 – 6.0 (mmol/L)	>6.0 – 7.0 (mmol/L)	>7.0 (mmol/L)	Death
Uric Acid (hyperuricemia) (high)	>ULN – 590 (umol/L)	—	—	>590 (umol/L)	—
Sodium, serum-low (hyponatremia)	130 - <LLN (mmol/L)	—	120 - <130 (mmol/L)	<120 (mmol/L)	Death
Sodium, serum-high (hypernatremia)	>ULN - 150 (mmol/L)	>150 - 155 (mmol/L)	>155 - 160 (mmol/L)	>160 (mmol/L)	Death
Urinalysis					
Proteinuria (high)	1+ proteinuria; urinary protein <1.0 g/24 hrs	≥2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs	urinary protein >=3.5 g/24 hrs	—	—

* Corrected serum calcium by albumin should be referred. If serum albumin is <4.0 g/dL, the corrected calcium will be calculated using the following formula:
Corrected calcium (mg/dL) = Total calcium (mg/dL) – 0.8 x [Albumin (g/dL) – 4]

13.2 Dose Assignment Using Modified Toxicity Probability Interval (mTPI) Design

Number of Subjects With DLT	Number of Evaluable Subjects at The Current Dose																		
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
0	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
1	**S**	**S**	**S**	**S**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
2	**D**	**D**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]	**S**	**S**	**S**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
3	**D,U**	**D,U**	**D,U**	**D**	**S**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**	**S**	**S**	**E**	**E**
4		**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]
5			**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D**	**S**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]
6				**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D**	**S**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]
7					**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**S**	**S**	**S**	**S**	**S**
8						**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**S**	**S**
≥9							**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**

E = Escalate to the next higher dose, S = Stay at the current dose, D = De-escalate to the next lower dose[b], U = Current dose is unacceptably toxic (ie, Do not re-enter the current dose)

Target DLT rate at MTD = 25%, its equivalence toxicity interval = 20 to 30%

Display for more than 21 subjects at the current dose is omitted.

a: Early MTD determination and initiation of exploring OBD candidate may be considered.

b: If a 100% or 50% dose escalation resulted in "D", then an intermediate dose level between pre- and post-dose escalation would be evaluated in the next cohort.

A beta distribution of Beta (1, 1) based on a beta/binomial hierarchic model was used for the prior distribution. When a posterior probability of being the target DLT rate of 25% is >95% at particular dose level, the relevant dose assignment is defined as "U".

If the Bayesian predictive probability that future dose assignments will be S is 80% or greater when 9 further subjects are added to a particular dose level, early MTD determination may be considered.

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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7130-J081-101
Study Protocol Title:	A phase 1 study of E7130 in subjects with solid tumors
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	anti-drug antibody
AE	adverse event
ATC	anatomical therapeutic chemical
$AUC_{(0\text{-}inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$AUC_{(0\text{-}t)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
BC	breast cancer
BLQ	below the limit of quantification
BOR	best overall response
BSA	body surface area
CBR	clinical benefit rate
CI	confidence interval
CL	total clearance
C_{max}	maximum observed concentration
C_{end}	concentration at end of infusion
C_{trough}	trough drug concentration of each cycle
CR	complete response
CRC	coloreactal cancer
CRF	case report form
CSR	clinical study report
CTCAE	common toxicity criteria for adverse events
CV	coefficient variation
DCR	disease control rate
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GC	gastic cancer
Her2	human epidermal growth factor receptor type2
HPD	highest posterior density
HPV	human papillomavirus
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximally tolerated dose

Abbreviation	Term
mTPI	modified toxicity probability interval
NE	not evaluable
OBD	optimal biologic dose
ORR	objective response rate
OS	overall survival
PAVA	pooled adjacent violators algorithm
PD	pharmacodynamics
PD	progressive disease
PFS	progression free survival
PGx	pharmacogenomics
PK	pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
PTF	peak-trough fluctuation
QT	QT interval
RD	recommended dose
RECIST	response evaluation criteria in solid tumor
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SD	stable disease
SI	système international
SOC	system organ class
SpO_2	percutaneous oxygen saturation
$t_{1/2}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TLG	tables, listings, and graphs
t_{max}	time at which the highest drug concentration occurs
UPM	unit probability mass
V_{ss}	volume of distribution at steady state
WHO DD	World Health Organization drug dictionary
λ_z	terminal phase rate constant

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 E7130-J081-101.

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the tolerability and safety profile of E7130 in subjects with advanced solid tumors.

3.1.2 Secondary Objectives

- To determine the maximally tolerated dose (MTD) of E7130 (only in Part 1).
- To evaluate the pharmacokinetics (PK) of E7130.
- To determine the recommended dose (RD) for future studies.
- To evaluate objective response rate (ORR), disease control rate (DCR) and clinical benefit rate (CBR).
- To evaluate progression-free survival (PFS) and the overall survival (OS) (only in Part 2).

3.1.3 Exploratory Objectives

CCI

[redacted]

3.2 Overall Study Design and Plan

3.2.1 Overall Study Design and Plan

This is a Phase 1 study of E7130 in subjects with advanced solid tumors. This study will be conducted in 2 parts (Part 1 and Part 2). Part 1 will be the dose escalation portion of this study to assess dose-limiting toxicity (DLT) and to determine the MTD in subjects with solid tumors. Considering efficacy, safety, PK and biomarker, up to 3 doses in 1 regimen either every 2 weeks or 3 weeks will be selected from Part 1 for Part 2. Part 2 will comprise cohort expansions to further characterize the safety and tolerability of E7130 and to evaluate

preliminary efficacy of E7130 in subjects with Her2-negative breast cancer (BC), followed by other solid tumors (squamous cell carcinoma of the head and neck [SCCHN] and other cancer, eg, gastric cancer [GC] and colorectal cancer [CRC]). After completion of Part 2, RD for future studies will be estimated based on the data from Part 1 and Part 2.

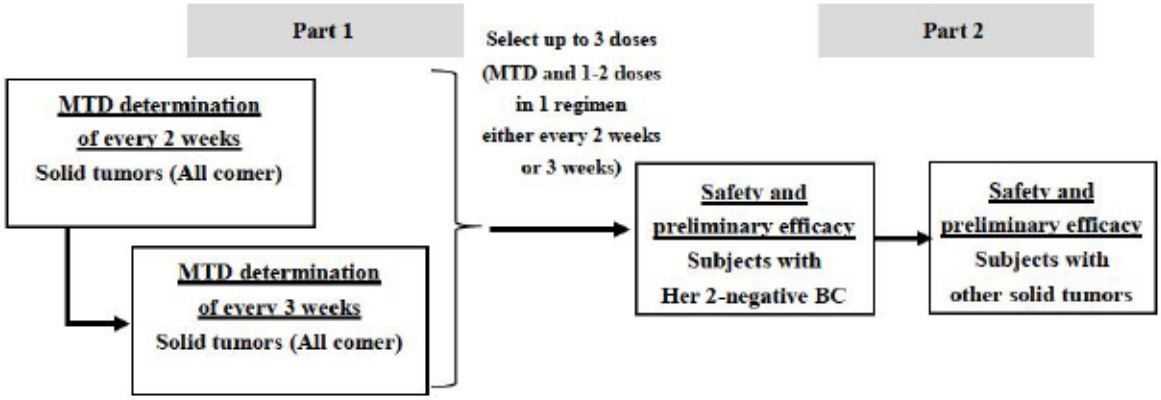


Figure 1 Overview of Study Design

3.2.2 Part 1

The study design overview of Part 1 is presented in Figure 2. Part 1 will be conducted in subjects with solid tumors. Part 1 will consist of a Pretreatment Phase, Treatment Phase, and Follow-up Phase.

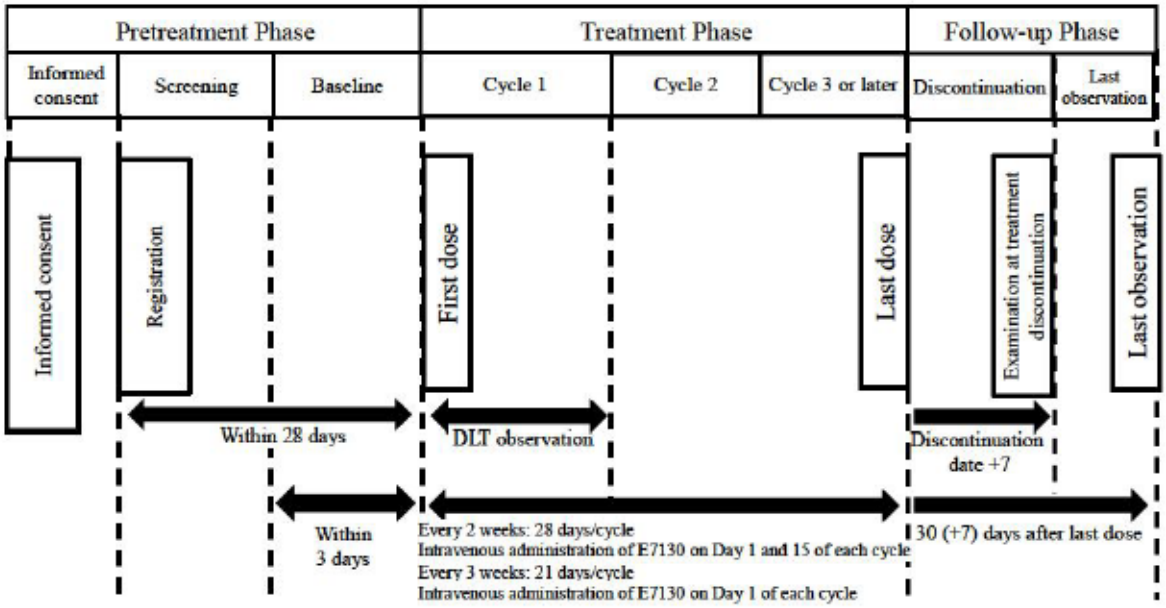


Figure 2 Overall Study design of Part 1

The Pretreatment Phase will involve obtaining informed consent, a screening period, and a

baseline assessment. The Treatment Phase will consist of Cycle 1 for DLT assessment with every 2 weeks and every 3 weeks regimen and subsequent cycles for sequence treatment. First, DLT assessment will be initiated to determine MTD with every 2 weeks. Once the first DLT with every 2 weeks regimen is observed, DLT assessment will be initiated to determine MTD with every 3 weeks at (-1) lower dose than the dose where the first DLT with every 2 weeks regimen was observed. Based on result of DLT assessment including PK profile with every 2 weeks regimen, DLT assessment with every 3 weeks regimen may be shifted before the first DLT with every 2 weeks regimen is observed. For Cycle 1 and onward, each cycle is 28 days long for every 2 weeks regimen and 21 days long for every 3 weeks regimen. In Cycle 1 and onwards, subjects will be administered E7130 every 2 weeks (Day 1 and 15 of each cycle) or every 3 weeks (Day 1 of each cycle) until they meet any of the criteria in "Criteria for discontinuation" of study protocol. The Follow-up Phase will consist of the examination at study discontinuation and the last observation period.

Dose assignment of subjects

An accelerated Modified Toxicity Probability Interval (mTPI) design (Ji Y and Wang SJ, 2013) will be employed to determine the MTD of E7130. Firstly, MTD of E7130 with every 2 weeks regimen will be determined in following manner. The initial dose level of E7130 with every 2 weeks regimen will be 25 $\mu g/m^2$ and the first cohort would enroll 3 subject for DLT evaluation. In the first cohort only, initial administration of E7130 for the second subject must be started on and after the 29th day after C1D1 of the first subject. If drug-related Grade 2 or higher toxicity is observed in 1 or more subjects within the initial cohort, dose assignment for following cohorts will be determined based on mTPI design, described below. If drug-related Grade 2 or higher toxicity is NOT observed in the initial cohort, DLT will be evaluated in successive dose level with single-subject until such a toxicity was observed. If such a toxicity is observed, the cohort will be expanded to enroll total 3 subjects.

After that, each subject will be assigned a dose of E7130 in accordance with the rules of the mTPI design based on a DLT rate of 25% and the corresponding 3 toxicity probability intervals that are defined as 20% to 30% (proper dosing), 0% to <20% (underdosing) and >30% to 100% (overdosing). The entire dose assignment decision rule can be precalculated under the mTPI design and presented in Table 1.

Table 1 Decision Rule for Dose Assignment

		Number of Evaluable Subjects at the Current Dose				
		3	6	9	12	15
Number of Subjects with DLT	0	**E**	**E**	**E**	**E**	**E**
	1	**S**	**S**	**E**	**E**	**E**
	2	**D**	**S**	**S**[a]	**S**	**E**
	3	**D, U**	**D**	**S**	**S**[a]	**S**[a]
	4		**D, U**	**D**	**S**	**S**[a]
	5		**D, U**	**D, U**	**S**	**S**
	6		**D, U**	**D, U**	**D, U**	**S**
	≥7			**D, U**	**D, U**	**D, U**

E = Escalate to the next higher dose, **S** = Stay at the current dose, **D** = De-escalate to the next lower dose [b], **U** = Current dose is unacceptably toxic (ie, Do not re-enter the current dose)

Target DLT rate at MTD = 25%, its equivalence toxicity interval = 20 to 30%, Cohort size = 3 subjects

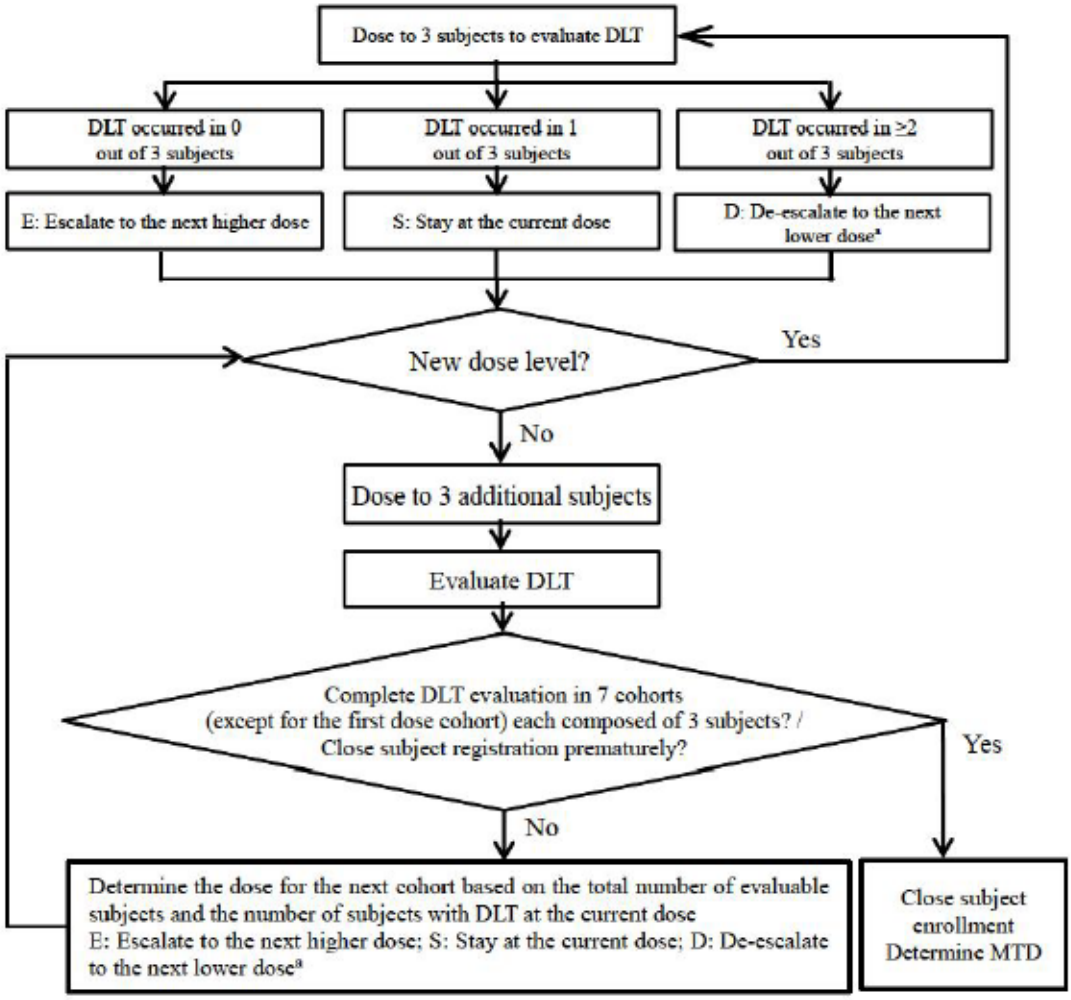
Display for more than 15 subjects at the current dose is omitted

a: Early MTD determination and initiation of exploring OBD candidate may be considered.

b: If a 100% or 50% dose escalation resulted in "D", then an intermediate dose level between pre- and post-dose escalation would be evaluated in the next cohort.

Based on the number of subjects developing DLT(s) during the DLT assessment period in each dose level, dose assignment (escalate, stay, de-escalate) for the next 3 subjects will be determined according to the above table. When 1 subject has already been evaluated in next dose, two subjects will be enrolled and dose assignment will be determined based on a result from the 3 subjects. In case where 4 or more subjects were enrolled and evaluated in a cohort, dose assignment (not shown in above table) will be determined by a result from all the subjects at the dose. Next cohort at the dose level will enroll and evaluate 2 or less subject so that the number of subjects at the dose level be multiples of 3. For example, if 4 subjects are treated and evaluated at once as 1 cohort and another cohort is assigned to the same dose, 2 subjects will be treated and evaluated as the another cohort. At the new dose level where 3 subjects (except for initial dosing cohort of every 2 weeks regimen) are enrolled, the second subject should start to receive the initial administration of E7130 on the following day after the first subject is observed in C1D1. Subjects who are not evaluable for DLT (for example, those subjects who discontinued during Cycle 1 for reasons other than DLT occurrence) should be replaced within their dose level. When DLT evaluation is completed in 7 cohorts being composed of 3 subjects (except for initial dosing cohort), MTD for every 2 weeks regimen will be determined and then "additional subjects to explore candidate OBD" (described later) will be enrolled. However, the maximum number of the cohort may be adjusted as required. In addition, early determination of MTD and start of exploring candidate OBD may be considered if the probability of future subjects also being

allocated to that dose is expected to be high enough. Details of the mTPI design are described in Section 5.3.6. Figure 3 shows the process of dose assignment to subjects based on Table 1.



a: If a 100% or 50% dose escalation resulted in "D," an intermediate dose level between the current dose and the next lower dose will be evaluated in the next cohort.

Figure 3 The Process of Dose Assignment

MTD in every 2 weeks regimen will be selected as the dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate based on the posterior distribution of DLT rate for each dose. Once MTD is selected in accordance with that way, we will finally determine MTD after toxicity data until Cycle 2 is taken into account. Once the first DLT with every 2 weeks regimen is observed, DLT assessment will be initiated to determine MTD with every 3 weeks at (–1) lower dose than the dose where the first DLT with every 2 weeks regimen was observed. Based on result of DLT assessment including PK profile with every 2 weeks regimen, DLT assessment with every 3 weeks regimen may be shifted

before the first DLT with every 2 weeks regimen is observed. The initial dose level of E7130 with every 3 weeks regimen will be decided based on safety profile in every 2 weeks regimen and the first cohort would enroll 3 subjects for DLT evaluation.

The dose assignment rule in every 3 weeks regimen is also determined by mTPI method, described above. To determine dose assignment in every 3 weeks regimen, the DLT evaluation result at a same dose level in every 2 weeks regimen will not be pooled. When DLT evaluation is completed in 5 cohorts being composed of 3 subjects, MTD for every 3 weeks regimen will be determined in the same step as every 2 weeks regimen and then "Additional subjects to explore candidate OBD" (described later) can be enrolled. However, the maximum number of the cohort may be adjusted as required.

If there are subjects who could not complete infusion of E7130 on C1D1 and C1D15 (only every 2 weeks regimen) or the DLT assessment during 28 days (every 2 weeks) / 21 days (every 3 weeks) period following first dose of E7130 because of any reasons except DLTs, the sponsor should discuss whether the subjects should be included in the DLT analysis population with the investigator, medical expert and if necessary, independent medical advisors. And based on the discussion, the sponsor could also replace DLT evaluable subjects enrolling additional subjects. In addition, transition to next dose levels and dose escalation range will be decided after also considering the safety data of those subjects who were excluded from the DLT analysis population.

Additional subjects to explore candidate OBD

In Part 1, during the escalation process to determine the MTD for the 2 weeks or 3 weeks regimen, selected doses at and below the MTD (up to 2 doses and MTD in each regimen) could be expanded with an additional 6 to 9 subjects (total 9 subjects per cohort) to obtain additional safety, efficacy, PK and biomarker data. Based on totality of preclinical and clinical information including safety and tolerability, PK, efficacy and biomarkers obtained in Part 1, 1 schedule regimen would be selected and the MTD and up to 2 lower doses (candidate OBDs) in selected regimen would be considered for Part 2 to explore the OBD in Her2(−) BC cohort. The OBD candidates at lower dose level than MTD from the 1 selected regimen only (every 2 weeks or 3 weeks) will be taken.

3.2.3 Part 2

Part 2 will consist of 2 steps - A and B, where in Step A, subjects with Her2(-) BC will be enrolled at MTD and up to 2 lower doses of 1 selected regimen either every 2 weeks or 3 weeks in Part 1. Each dose level consists of 20 subjects. Based on the totality of information in this cohort, further cohorts may be enrolled to determine the OBD based on all safety, PK, biomarker data and efficacy data in specific tumor types. Tumor types considered in this Step B are SCCHN, and other cancers (eg, CRC, GC). Each dose level consists of 10 subjects.

Subjects with Her2-negative BC and other solid tumors (SCCHN, GC and CRC) will be evaluated in Part 2. Part 2 will consist of a Pretreatment Phase, a Treatment Phase, and a Follow-up Phase. The Pretreatment Phase will involve obtaining informed consent, a screening period, and a baseline assessment. The Treatment Phase will consist of treatment cycles that are each 28 days (every 2 weeks regimen) or 21 days (every 3weeks regimen) in duration, and administration of E7130 every 2 weeks or 3 weeks will continue until subjects meet any of the criteria in "Criteria for discontinuation" of study protocol. The Follow-up Phase will consist of the examination at study discontinuation, the final observation and the follow-up for PFS and OS. In the follow-up for PFS and OS, subject's survival and post-anti-cancer treatment, if requested by the sponsor, will be followed (eg, 6, 12, 18 months after the last subject's enrollment) until the sponsor terminates the study, the followed last subject is death/lost to follow-up/withdraws his or her consent, or 18 months after the last subject's enrollment, whichever comes first.

4 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to evaluate the tolerability and safety profile of E7130. The number of subjects in the Part 1 will be approximately 70. For every 2 weeks regimen, if drug-related Grade 2 or higher toxicity is not observed in 3 subjects at initial dosing cohort, some subjects will be enrolled in single-subject cohort and then 7 cohorts of 3 subjects (except for initial dosing cohort in every 2 weeks regimen) will be investigated after increasing of cohort size from 1 to 3. Five cohorts of 3 subjects will be investigated in dose finding of every 3 weeks regimen. The maximum number of the cohort in mTPI parts may be adjusted if necessary. The maximum sample number of cohort for each regimen was deemed appropriate to explore some dose levels around MTD, and evaluate their safety profile. After dose finding with mTPI design, approximately 30 subjects will be enrolled for exploring candidate OBD purpose.

The Part 2 by 10-20 subjects each dose of each tumor cohort will allow for further evaluation of safety and preliminary anti-tumor activity. The numbers of subjects were mainly based on the feasibility of enrollment. For illustrative purposes, if there are no objective responses on ≥20 subjects, where the probability is ≤12.2 % under ORR of 10 %, the dose level of E7130 might be considered unpromising for this population, unless the clinical judgment suggested otherwise.

5 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the data cutoff for analysis or the study is completed and the database is locked. Statistical analyses will be performed using SAS software or other validated statistical software as required.

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

All statistical analysis will be performed by part separately. Every 2 weeks and 3 weeks regimen are not pooled on summarization in Part 1. The cancer cohort in Part 2 other than BC or SCCHN will be defined by actually enrolled cancer (eg. GC, CRC, etc.).

The results of other biomarker analyses will be reported separately, and the details of these analyses will be described in a separate analysis plan.

5.1 Study Endpoints

5.1.1 Primary Endpoints

- **Tolerability endpoint:** DLTs.
- **Safety endpoints:** AEs, clinical laboratory tests, vital signs, arterial oxygen saturation, body weight, 12-lead ECGs, and ECOG PS.

5.1.2 Secondary Endpoints

- **MTD determination:** will be selected as the dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate based on the posterior distribution of DLT rate for each dose. Toxicity data until Cycle 2 is taken into account to finally determine MTD.
- **Pharmacokinetic endpoints:** The endpoints are PK parameters derived by noncompartmental analysis using the plasma concentration–time data of E7130, including followings but not limited to: maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), area under the concentration–time curve (AUC), terminal elimination phase half-life ($t_{1/2}$), total clearance (CL), and distribution volume (V_d). The amount of unchanged drug excreted in urine and feces and renal clearance(CL_R) will be derived, if possible in subjects who have urine and feces samples in Part1.
- **RD:** The RD is determined based on the MTD, the OBD and efficacy/safety/PK/PD data in Part 1 and Part 2.
- **Efficacy endpoints:** Best overall response (BOR) based on RECIST 1.1, objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR), PFS, OS and percent changes from baseline in the sum of the diameters of tumor target lesions (if applicable).

BOR is complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), and not evaluable (NE), where SD has to be achieved at ≥5 weeks after first dose. CR or PR in Part 1 of this study requires no confirmation of the next response at ≥4 weeks. The confirmation is mandatory in Part 2.

ORR is defined as a proportion of subjects with BOR of CR or PR.

DCR is defined as the proportion of subjects with BOR of CR, PR or SD.

CBR is defined as the proportion of subjects with BOR of CR, PR or durable SD (duration of SD ≥ 23 weeks). Duration of SD is defined as the time from the date of first dose to the date of the first documentation of disease progression or death from any cause, whichever occurs first. It will be calculated for subjects whose BOR is SD.

PFS is defined as the time from the date of first dose to the first documented date of event (disease progression or death from any cause, whichever occurs first).

OS is defined as the time from the date of first dose to the date of death from any cause. For the subjects who are alive or unknown, OS is censored as the date of last known alive date or the date of data cut off, whichever comes first.

5.1.2.1 Pharmacokinetic (PK) Endpoints

PK parameters derived by non-compartmental analysis using plasma, urine, and fecal concentrations of E7130 which include, but are not limited to, are shown as below:

<Plasma PK Parameter>

Cycle 1 Day 1 and Cycle 2 Day 1

C_{max}	maximum observed concentration
t_{max}	time at which the highest drug concentration occurs
$AUC_{(0\text{-}t)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
$AUC_{(0\text{-}inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$t_{½}$	terminal elimination phase half-life
CL	total clearance
MRT	mean residence time
λ_z	terminal phase rate constant

V_{ss}	volume of distribution at steady state

Cycle 1 Day 15, Cycle 2 Day 15 (2 weeks regimen only), and Cycle 3 or later

C_{max}	maximum observed concentration
C_{end}	concentration at end of infusion
C_{trough}	trough drug concentration of each administration interval

<Urinary and fecal PK Parameter>

$A_{e(0-t)}$	amount of unchanged drug excreted in urine (or feces) up to time of last quantifiable urinary concentration (after dosing at time 0)
$A_{e(0-x)}$	amount of unchanged drug excreted in urine (or feces) up to fixed time of x (after dosing at time 0)
$A_{e(t1-t2)}$	amount of unchanged drug excreted in urine (or feces) between 2 data points t_1 and t_2
Fe	fraction of dose excreted in urine (or feces)
CL_R	renal clearance

5.1.3 Exploratory Endpoints

CCI [redacted]

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The DLT Analysis Set is the group of subjects in the Part 1 who completed Cycle 1 treatment of the study drug and were evaluated for DLT, and those who developed DLT during Cycle 1. This will be the analysis set for MTD determination in the Part 1.

The Safety Analysis Set is the group of subjects who received at least 1 dose of the study drug.

The Pharmacokinetic Analysis Set is the group of subjects who received at least 1 dose of the study drug and whose at least 1 postdose sample of blood was taken for PK analysis.

The Efficacy Analysis Set is the group of subjects who received at least 1 dose of the study drug and had both baseline and at least 1 postbaseline tumor assessments.

The PD and PGx Analysis Set is the group of subjects who received at least 1 dose of the study drug and had at least 1 PD and/or PGx data.

The number of subjects entered into Treatment Phase, the number and the percentage of subjects included in each analysis set will be presented. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized by each dose in each cancer cohort, by each cancer cohort (ie. dose will be pooled within each cancer cohort), and for whole subjects. Subject data listings will be provided.

5.2.2 Subject Disposition

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

Subject disposition table will include the number of subjects who were treated/not treated, and completed/discontinued the study. Similarly, the number of subjects who completed/discontinued the study treatment, and the primary reason for the study treatment discontinuation will also be summarized. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized by each dose in each cancer cohort, by each cancer cohort, and for whole subjects.

A subject who completed the study is defined as whose last observation had been done. A subject who completed the study treatment is defined as who discontinued study treatment due to disease progression or study cut-off.

Subject data listings will be provided.

5.2.3 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock. The protocol deviations identified according to the criteria at study entry and during treatment will not be included in TLGs covered by SAP, but will be presented in the clinical study report (CSR).

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in Safety Analysis Set. If the subjects included in PK Analysis Set is different from those who are in Safety Analysis Set, summarization on PK Analysis Set will be also performed. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized by each dose in each cancer cohort, by each cancer cohort, and for whole subjects.

Continuous demographic and baseline variables include

- Age
- Height
- Weight
- BMI
- Body surface area

Categorical demographic and baseline variables include

- Age group (< 65 years, ≥ 65 years)
- Sex
- Race
- Ethnicity
- ECOG-PS

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

- Primary tumor
  - For BC subjects, status of Her2 expression, estrogen receptor, and progesterone receptor are also summarized (positive, negative).
  - For SCCHN subjects, status of infection of human papillomavirus (HPV) is also summarized (positive, negative).
  - For GC subjects, status of Her2 expression is also summarized (positive, negative).
  - For colorectal cancer subjects, status of KRAS, NRAS, and BRAF mutation are also summarized (positive, negative).
- Tumor staging at diagnosis
- Known gene mutation status (positive, negative)
- Biomarker status in tumor tissue (positive, negative)
  - CD31, α-SMA positive cancer associated fibroblast, acetylated α-tubulin in tumor tissue
- Time from first diagnosis to the date of first study treatment (months) (as continuous variable)
- Involved disease organ
- Number of involved disease organ (1, 2, ≥3)
- Number of previous anticancer medication as regimen (1, 2, ≥3)
- Subjects with any previous radiotherapy
- Subjects with any previous anti-cancer procedure

Subject data listings will be provided.

Medical History

A subject data listing of medical history and current medical condition will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Prior medications will be defined as medications that stopped before the first dose of study treatment. Concomitant medications will be defined as medications that (1) started before the first dose of study treatment 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 treatment up to 30 days after the subject's last dose or up to the start date of new anticancer agents, whichever comes first. Medications received after 30 days of last dose or start date of new anticancer medication will be considered as post treatment medications.

The number (percentage) of subjects who took prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class (anatomical class, pharmacological class), and WHO DD preferred term on the Safety Analysis Set. The results will be summarized by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized by each dose in each cancer cohort, by each cancer cohort, and for whole subjects. For Part 2, the number (percentage) of subjects who received previous anti-cancer medication will be summarized in same manner.

Non-pharmacological procedures will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1 or later).

All medications and non-pharmacological procedures will be presented in subject data listings.

5.2.6 Treatment Compliance

Subjects with treatment related protocol deviations will not be included in TLGs, but presented in CSR as provided in Section 5.2.3.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

No adjustment for covariates will be performed.

5.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

5.3.4 Examination of Subgroups

The subgroup analyses will be performed, if deemed appropriate. The definition of subgroup will be determined and documented in SAP before database locked.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

The details of handling of missing data will be described in the section 8.

5.3.6 Other Considerations

Accelerated mTPI Design

An accelerated mTPI design will be employed to determine the MTD of E7130. When a drug-related Grade ≥2 toxicity is not observed in the first dose cohort (3 subjects) of every 2 weeks regimen, dose will be escalated in successive cohorts by single-subject DLT assessment until such a toxicity is observed. If such a toxicity is developed, the cohort will be expanded to evaluate DLT in 3 subjects and mTPI design with cohort size of 3 will be adopted.

The mTPI design uses a Bayesian statistical framework and a beta/binomial hierarchic model to compute the posterior probabilities of three intervals that reflect the relative distance between the DLT rates of each dose level to the target DLT rate of 25%.

Decision rules for dose-finding are based on calculating the unit probability mass (UPM) of three intervals corresponding to 0 to <20% (underdosing), 20 to 30% (proper dosing) and >30 to 100% (overdosing) in terms of toxicity. The UPM for each interval is defined as the probability of the interval divided by the length of the interval, and the one with the largest UPM implies the decision for future dose level to be assigned, i.e., 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 precalculated and presented.

Determination of MTD

MTD will be determined when the lowest dose has a >95% posterior probability of being DLT rate >25% (i.e., unacceptable DLT rate beyond the target DLT rate) or a prespecified maximum sample size, 7 or 5 cohorts being composed of 3 subjects in every 2 weeks or every 3 weeks regimen respectively (except for initial dosing cohort in biweekly regimen), is reached. However, the maximum sample size will be adjusted as necessary according to the actual number of dose levels that will be evaluated and the number of subjects evaluable for DLT. In addition, if the Bayesian predictive probability that future dose assignments will be S is 80% or greater (in other words, if it is considered highly likely that future registered subjects will also be assigned to the current dose level) when 9 further subjects are added to a particular dose level, subject registration will be closed early and the MTD can be determined.

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 ≤95% posterior

probability of being DLT rate >25%. Toxicity data until Cycle 2 is taken into account to finally determine MTD. 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, D, 1983) will be used to maintain monotonically increase of DLT rate with increasing dose level.

5.4 Efficacy Analyses

Efficacy analyses will be conducted based on the Efficacy Analysis Set. The results will be summarized by each dose group in Part 1. The results in Part 2 will be summarized by each dose in each cancer cohort, and by each cancer cohort.

5.4.1 Primary Efficacy Analyses

Since this trial is phase 1, primary efficacy endpoint is not defined.

Part 1

Based on the tumor assessments according to RECIST v1.1, BOR will be summarized. If a subject had a best overall response of non-CR/non-PD, the subject's best overall response will be grouped with the SD category. ORR, DCR, CBR and its corresponding exact 2-sided 95% confidence intervals will be calculated.

A waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir (ie, maximum tumor shrinkage). A spider plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions.

Part 2

Besides the similar analyses for the Part 1, PFS and OS will be summarized.

PFS is defined as the time from the date of first dose to the date of first documented PD or death due to any cause (whichever occurs first) and calculated as below. For subjects who did not have an event, PFS will be censored. Censoring rules for PFS are shown in Table 2.

PFS (months) = (Date of first documented PD/ death/ censored date – Date of first dose + 1) / (365.25/12).

The cumulative PFS rate will be calculated using Kaplan-Meier method. The median, Q1, and Q3 for PFS with their 95% CIs will be evaluated. The 95% CIs will be calculated based on Greenwood formula and log-log transformation. The number (percentage) of subjects with event/censored will be summarized. The PFS rate with its 95% CI at 6, 12, 18, 24, 36, 52, 78, and 104 weeks will also be calculated, but not limited to these time points. Kaplan-Meier plots with the number of subjects at risk will be presented.

OS is defined as the time from the date of first study dose to the date of death from any cause and calculated as below. Subjects who were lost to follow-up and the subjects who were alive at the date of data cutoff will be censored at the date the subject was last known alive or the cut-off date, whichever comes earlier. Censoring rules for OS are shown in Table 3. OS will also be summarized in the same manner as with PFS.

OS (months) = (Date of death/ censored date – Date of first dose + 1) / (365.25/12).

A swimmer plot will be presented for the PFS of each subject. A waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir (ie, maximum tumor shrinkage) with PFS of each subject will be presented in one figure.

Subject data listings will be provided.

Table 2 Censoring rules for PFS

No.	Situation	Date of Event or Censoring	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	Progression documented at scheduled visit	Date of first radiologic PD assessment	Event
3	Progression documented between scheduled visits	Date of first radiologic PD assessment	Event
4	No progression nor death at the time of data cut-off or discontinuation from study treatment	Date of last adequate radiologic assessment* prior to or on date of data cut-off or discontinuation from study treatment	Censored
5	New anticancer treatment started	Date of last adequate radiologic assessment* prior to or on date of new anticancer treatment	Censored
6	Death before first PD assessment	Date of death	Event
7	Death between adequate assessment visits*	Date of death	Event
8	Death or progression after two or more consecutive missed visit/tumor assessment**	Date of last adequate radiologic assessment* before missed tumor assessments	Censored

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than 182 days (ie. 12 weeks x 2 + 2 weeks [allowance of tumor assessment]) for subjects on the every 12-week scanning schedule in this study after Week 24.

The priority of the censoring rules is as follows:

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

- If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of first dose. However, if the subject died within 56 days (8 weeks) after the first dosing date and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
- If a subject had new anticancer treatment before PD or death (No. 5), the subject will be censored on the date of the last adequate tumor assessment prior to or on the date of new anticancer treatment.
- If a subject missed two or more assessments consecutively before PD or death (No. 8), the subject will be censored on the date of the last adequate tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criteria, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, 3, 6, 7), 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, 4, 5, 8).

Table 3 Censoring rules for OS

No.	Situation	Date of Event or Censoring	Outcome
1	Death before or on data cut off	Date of Death	Event
2	Death after data cut off	Date of data cut off	Censored
3	Subject still alive at data cut off	Date of data cut off	Censored
4	Subject lost to follow-up or withdraw of consent before data cut off	Date last known to be alive	Censored

5.4.2 Secondary Efficacy Analyses

Not applicable.

5.4.3 Other Efficacy Analyses

For evaluated tumot marker parameters, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using summary statistics. Spaghetti plot will be also presented for each subject. The percent change from baseline will also be used if deemed necessary.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The PK Analysis Set will be used for individual listings and the summaries of E7130 plasma, urinary, and fecal concentrations and for summaries and listings of PK parameters.

In Part 1 of this study, using non-compartmental analysis, plasma concentrations of E7130 will be analyzed to determine the PK parameters including C_{max}, t_{max}, AUC, $t_{½}$, CL, and V_d. Urinary and fecal concentrations of E7130 will be analyzed to determine the PK parameters including amount of unchanged drug excreted in urine or feces and renal clearance (CL_R) in subjects who have urine and feces samples in Part1, if possible. Plasma concentration data in Part 2 of this study will be used to population PK analysis integrating plasma concentration data from Part 1 and other future studies. For population PK analysis, the details will be described in the separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

5.5.1.1 Plasma Concentrations and its PK Parameter Analysis

<Plasma Concentration>

Plasma concentrations of E7130 will be summarized using summary statistics (n, mean, SD, median, minimum and maximum) by each dose group separately by regimen (every 2 weeks/every 3 weeks) and nominal time points. Plasma concentrations of E7130 will be listed for each subject by each dose group separately by regimen, and actual sampling time.

<Plasma PK Parameter>

PK parameters will be derived by noncompartmental analysis using Phoenix WinNonlin software (version 6.2.1 or later) according to Eisai non-compartmental pharmacokinetic Analysis Manual (302-104.00-MNL). The following PK parameters for E7130 will be calculated:

Cycle 1 Day1 and Cycle 2 Day 1

C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $t_{½}$, MRT, λ_z, CL, V_{ss}

Cycle 1 Day 15, Cycle 2 Day 15 (2 weeks regimen only)

C_{max} and C_{trough}

Cycle 3 or later

C_{end} and C_{trough}

Other PK parameters may be calculated as appropriate. For each dose group separately by regimen, summary statistics will be tabulated for the PK parameters. Summary statistics (n, mean, SD, median, minimum and maximum) will be presented for all parameters (apart from

t_{max} where mean and SD are not required). In addition, geometric mean and %CV will also be presented for all parameters apart from t_{max}.

PK parameters of E7130 for each subject will be listed.

5.5.1.2 Urine and Fecal Concentration and its PK Parameter Analysis

Urine volume and urinary concentrations of E7130 and fecal weight and fecal concentrations of E7130 will be listed for each subject by each dose group separately by regimen and actual sampling time.

The following urinary and fecal PK parameters will be derived by SAS and/or Phoenix WinNonlin according to 302-104.00-MNL.

Cycle 1 Day 1

<Urinary PK parameter>

Amount of E7130 recovered in urine ($A_{e(t1\text{-}t2)}$) by each collection interval

Cumulative amount of $A_{e(t1\text{-}t2)}$ in urine until end of each collection interval ($A_{e(0\text{-}x)}$) and total collection period ($A_{e(0\text{-}t)}$)

Fraction of dose excreted (Fe; % of dose) in urine by each collection interval

Cumulative Fe in urine until end of each collection interval and total collection period

Renal clearance (CL_R) [CL_R will be obtained as $CL_R = A_{e(0\text{-}t)}/AUC_{(0\text{-}t)}$]

<Fecal PK parameter>

Amount of E7130 recovered in feces ($A_{e(t1\text{-}t2)}$) by each collection interval

Cumulative amount of $A_{e(0\text{-}x)}$ in feces until end of each collection interval and total collection period ($A_{e(0\text{-}t)}$)

Fraction of dose excreted (Fe; % of dose) in feces by each collection interval

Cumulative Fe in feces until end of each collection interval and total collection period

Summary statistics (n, mean, SD, median, minimum and maximum) will be tabulated for the urinary and fecal PK parameters of E7130 respectively by each dose group combined regardless of regimen and separately by regimen, and collection period.

Urinary and fecal PK parameters of E7130 for each subject by each dose group combined regardless of regimen and separately by regimen will be listed.

<Total (urine and feces)>

Summary statistics (n, mean, SD, median, minimum and maximum) will be tabulated for sum of cumulative Fe in urine and feces until end of each collection interval and total collection period by each dose group combined regardless of regimen and separately by regimen.

5.5.1.3 Pharmacokinetic Data Figures

<Plasma Concentration>

The following figures will be displayed separately by regimen.

Linear and semi-log plots of mean E7130 plasma concentration-time profiles of all dose groups will be displayed in the same graph using nominal time with SD by Cycle (Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing).

Linear and semi-log plots of mean E7130 plasma concentration-time profiles after Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing will be displayed using nominal time by each dose group in the same graph.

Linear and semi-log plots of E7130 plasma concentration-time profiles of all subjects by each dose group will be displayed using actual time by Cycle (Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing).

Linear and semi-log plots of E7130 plasma concentration-time profiles after Cycle 1 Day1 dosing and Cycle 2 Day 1 dosing will be displayed using actual time by individual subject.

The individual and mean (±SD) plasma trough concentrations of E7130 will be displayed using the nominal time in linear scale.

The individual and mean (±SD) C_{end} of E7130 will be displayed using the nominal time in linear scale.

<Urine and fecal PK parameters>

Mean cumulative Fe until end of each collection interval and total collection period in urine, feces, and urine and feces totally will be plotted by each dose group combined regardless of regimen and separately by regimen.

5.5.1.4 Evaluation of Dose-Proportionality in PK Parameters

The PK Analysis set will be used for evaluation of dose proportionality. This will be applicable where there are PK parameters of at least 3 dose levels separately by regimen. The dose proportionality for E7130 will be investigated using PK parameters obtained from non-compartmental analysis after Cycle 1 Day 1 dosing.

Doses ($\mu g/m^2$) will be plotted on the X axis and each parameter (C_{max}, $AUC_{(0\text{-}t)}$, and $AUC_{(0\text{-}inf)}$) will be plotted on the Y axis to display the data of all subjects.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

The results of other biomarker analyses will be reported separately, and the details of these analyses will be described in a separate analysis plan.

5.5.3 Pharmacokinetic / Pharmacodynamic Analyses

Plasma E7130 concentration and electrocardiogram (ECG) analyses will be performed based on the Safety Analysis Set. PK–QT interval relationships between plasma E7130 concentration and QT/QTcF will be evaluated graphically.

Individual ΔQTcF is calculated as QTcF on Day 1 or later minus the time-matched QTcF on Day-1 or earlier.

Individual ECG parameter (QTcF or ΔQTcF) values at each time point will be plotted against plasma E7130 concentration collected at the same time point by each dose group in the same graph separately by regimen.

Mean(±SD) ΔQTcF values at each time point will be plotted against Mean(±SD) plasma E7130 concentration collected at the same time point by each dose group to evaluate hysteresis effect separately by regimen.

5.6 Safety Analyses

DLT analyses will be performed on the DLT Analysis Set by each dose group and for total dose groups. The Safety Analysis Set will be used for all other safety analyses. The safety analysis will be performed by each dose group and for total dose groups in Part 1. The results in Part 2 will be summarized by each cohort, by each cancer cohort, and for whole subjects. Safety data will be summarized on an "as treated" basis using summary statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; number [percentage] for categorical variables).

5.6.1 Extent of Exposure

For every 2 week regimen, the parameters to be summarized are defined as follows.

- Number of cycles = The last cycle with study drug dosing
- Duration of treatment (days) = Date of Day 1 of the last cycle with study drug dosing + 28 – first dosing date
- Duration of treatment (months) = (Date of Day 1 of the last cycle with study drug dosing + 28 – first dosing date) / (365.25/12)
- Number of subject-month with study drug dosing = Sum of duration of treatment (months) per subjects
- Total doses ($\mu g/m^2$) = Sum of all the actual dose derived by;
  (Planned dose of each cycle [$\mu g/m^2$]) x (Actual volume infused [ml] / volume to be infused [ml])
- Dose intensity ($\mu g/m^2$/4weeks) = Total doses / (Duration of treatment [days] / 28)
- Relative dose intensity (%) = 100 × Dose intensity / Planned dose in Cycle 1 ($\mu g/m^2$)

For every 3 week regimen, the parameters to be summarized are defined as follows.

- Number of cycles = The last cycle with study drug dosing
- Duration of treatment (days) = Date of Day 1 of the last cycle with study drug dosing + 21 – first dosing date
- Duration of treatment (months) = (Date of Day 1 of the last cycle with study drug dosing + 21 – first dosing date) / (365.25/12)
- Number of subject-month with study drug dosing = Sum of duration of treatment (months) per subjects
- Total doses ($\mu g/m^2$) = Sum of all the actual dose derived by;
  (Planned dose of each cycle [$\mu g/m^2$]) x (Actual volume infused [ml] / volume to be infused [ml])
- Dose intensity ($\mu g/m^2$/3weeks) = Total doses / (Duration of treatment [days] / 21)
- Relative dose intensity (%) = 100 × Dose intensity / Planned dose in Cycle 1 ($\mu g/m^2$)

The number (percentage) of subjects who experienced dose interruption (ie. permanent or temporary stopping administration during an infusion), dose delay (ie. postponing the next dosing), dose reduction will be provided. When "Actual volume infused" is less than "volume to be infused" in a cycle, or "Infusion Speed" contains 0, they are considered as dose interruption event. For every 2 week regimen, the following two cases are considered as dose delay event; 1) Cycle X Day 15 is more than 14 days after Cycle X Day 1, 2) Cycle X + 1 Day 1 is more than 21 days after Cycle X Day 15. For every 3 week regimen, when a successive cycle starts more than 28 days after the previous cycle Day 1, it is considered as dose delay event. When a planned dose is less than previous one, it is considered as dose reduction event.

In addition, cycle of first dose reduction (2, 3, 4, 5, >=6) and frequency of dose reduction (0, 1, 2, >=3) is summarized.

Subject data listings will be provided.

5.6.2 Adverse Events

DLTs (Part 1 only)

The number (percentage) of subjects who experienced DLT will be summarized. DLT will also be summarized by below criteria as reported in CRF.

- Febrile neutropenia
- Grade4 neutropenia that persists for more than 7 days or any neutropenia that requires hematopoetic stimulating agents.
- Grade 4 thrombocytopenia, or thrombocytopenia that requires platelet transfusion
- Grade 4 anemia, or anemia that requires blood transfusion.
- Any Grade 3 or higher non-hematological toxicity with the exception of abnormal clinical laboratory values with no clinical significance, or any events which can be managed and controlled to Grade 2 or less by maximal medical management
- Any Grade 4 non-hematological toxicity
- In every 2 week regimen, development of any toxicity that is considered to be related to E7130 and where dose skip at C1D15 is necessary.
- In every 3 week regimen, development of any toxicity that is considered to be related to E7130 and where dose at C2D1 is necessary to postpone for over 14 days for recovery from the toxicities

The estimates of DLT rate based on Bayesian statistics will be provided using non-informative beta prior distribution of Beta (0.005, 0.005) by each dose. The estimates will include posterior mean, median, mode (if applicable), variance, standard deviation, 95% highest posterior density (HPD) credible interval, probability of > 25%, 0 - 20%, 20 - 30%

and 30 - 100%. If the posterior mean does not increase monotonically, adjusted mean using the PAVA, weighted by the number of patients in each dose, will also be shown.

All DLTs will be presented in subject data listings.

Adverse events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA version 20.1 or later). Adverse events will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE), defined in the section 8.3, will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-related TEAEs include those events considered by the investigator to be related to study treatment.

A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

An overview table, including the incidence of and the number of subjects with TEAEs, Treatment-related TEAEs, TEAEs with grade 3 or above, serious adverse events (SAEs), deaths, and TEAEs that led to discontinuation, dose reduction and, dose interruption of study treatment will be provided based on the report in AE form of CRF.

The incidence of below events will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT.

- TEAEs
- TEAEs by the highest CTCAE grade
- TEAEs grade 3 or above
- Serious TEAEs
- Treatment-related TEAEs
- Treatment-related TEAEs by the highest CTCAE grade
- Treatment-related TEAEs grade 3 or above
- Treatment-related serious TEAEs
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to dose reduction of study treatment
- TEAEs leading to dose interruption of study treatment

All deaths will also be summarized by primary reasons of deaths (progressive disease, AEs, others), deaths within 30 days of last dose, deaths >30 days of last dose, and treatment-related deaths.

Subject data listings of all deaths, SAEs, AEs leading to death, discontinuation of study treatment, dose reduction of study treatment and dose interruption of study treatment will be provided.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters, the actual value and the change from baseline to each postbaseline visit will be summarized by visit using summary statistics. Qualitative parameters will be summarized by number and percentage of subjects, and changes from baseline to each postbaseline visit will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Box plot display will be used to show the longitudinal change of actual data of the parameters by visit.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value is below (L), within (N), or above (H) the laboratory parameter's reference range. The result of LNH classification will be provided in a subject data listing.

Laboratory parameters will be graded by CTCAE ver. 4.03 in the section 13.1. Changes from CTCAE grade at baseline to each postbaseline visit and worst postbaseline will be reported using shift tables. CTCAE will also be used to identify subjects with Treatment-emergent markedly abnormal laboratory value (TEMAV). The number (percentage) of subjects with TEMAV (markedly abnormal high/low) will be summarized for each visit and overall study period. The changes from baseline to each postbaseline visit and overall study period will also be reported using shift tables. The TEMAV will be defined in the section 8.3.

Subject data listing will be provided.

5.6.4 Vital Signs

Summary statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, respiratory rate, and temperature), weight, and SpO_2 and changes from baseline will be presented by visit.

Box plot display will be used to show the longitudinal change of actual data of the parameters by visit.

Subject data listings will be provided.

5.6.5 Electrocardiograms

Part 1

Summary statistics for ECG parameters (Heart Rate, RR, PR, QRS, QT, and QTcF) and changes from baseline will be presented by time point. For cycle 1 and 2, the results assessed at same time points (ie. before dose, 10 minute after end of infusion, 2 hours after end of infusion, 4 hours after end of infusion) in baseline assessment will be used as the baseline data and change from baseline will be calculated. For cycle 3, 5, and 8, the assessment time points are before dose and 10 minute after end of infusion. The calculation of change from baseline will follow same manner. If the relevant baseline data is missing, the change from baseline will also be calculated as missing.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each visit.

In addition, the number (percentage) of subjects who met below criteria at least one postdose abnormal ECG result in QTcF measured at the external ECG assessment organization will be presented:

Absolute QTcF interval prolongation:

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

Change from baseline in QTcF interval:

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

Part 2

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each visit.

Subject data listings will be provided.

5.6.6 Other Safety Analyses

ECOG PS

The number (percentage) of subjects for each category of ECOG PS will be summarized by visit. The highest postbaseline scale of ECOG PS for each subject will also be summarized.

Subject data listings will be provided.

5.7 Other Analyses

No other analysis is planned for this study.

5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

A summary of all major additions, changes and deletions in the planned analyses described in the protocol will be provided in this section.

- Waterfall and spaghetti plot will be generated in Part 1 also.
- Tumor marker will be summarized as an exploratory endpoint.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

8.1 General Data Handling

Definition of Baseline data

Except for electrocardiograms assessment in Part 1, baseline is defined as the last non-missing value observed prior to the first dose of study treatment for a given parameter.

The definition of baseline data for electrocardiograms in part 1 is shown in Section 5.6.5.

Definition of Change from Baseline, Percent Change from Baseline

Change from baseline is defined as post-baseline value minus baseline value.
Percent change from baseline is defined as follows:

% Change from baseline = (Change from baseline / Baseline) * 100%

For any Baseline value of 0, the subject's corresponding percent change from baseline will not be included in the summary statistics table.

Calculation of Body Surface Area

Du Bois method will be sued to calculate body surface area (BSA).

BSA (m^2) = $height^{0.725}$ (cm) * $weight^{0.425}$ (kg) * 0.007184

8.2 Efficacy Data Handling

Handling of missing data for tumor assessment result

For the calculation of ORR, DCR and CBR, subjects with missing response status (subjects whose baseline is missing and/or no adequate post-baseline tumor assessments result) will be not included in numerator, but included in denominator.

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

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

8.3 Safety Data Handling

Treatment-emergent adverse event

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during the time from the first dose of study drug to 30 days following the last dose of study drug or the start date of new anticancer agents (whichever comes first), having been absent at pretreatment (Baseline) or

- Reemerged during treatment, having been present at pretreatment but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

Adverse Events

Adverse Events with incomplete start dates will be considered treatment emergent 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;

d. Year is missing;

e. Complete date is missing.

Concomitant Medications

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;

e. Complete date is missing.

TEMAV (Treatment-Emergent Markedly Abnormal Value)

Treatment-emergent markedly abnormal laboratory value (TEMAV) is defined as a postbaseline laboratory value with grade 3 or higher, and with a grade increase from baseline. (ie., Increasing grade 0 to 3 or higher, grade 1 to 3 or higher, grade 2 to 3 or higher, grade 3 to 4 or 5, grade 4 to 5.)

Handling of below lower quantification values in laboratory results

In the cases where laboratory result contains below lower quantification (BLQ) value, it will be replaced to the lower limit value of quantification (LLOQ) for summary tables.

Visit Windows

The purpose of visit windows is to provide a single record per subject per visit for the calculation of descriptive statistics for safety parameters (e.g., laboratory values and vital signs, etc.) per scheduled visit, and change from baseline per visit. Other safety analyses (e.g., worst grade laboratory results) will include all observations.

The observation closest to the target date will be used in by visit summaries. If two or more observations have the same distance to the target visit day, the one that has the highest CTCAE grade or is furthest away from the normal range will be used for summary tables. If the multiple data in the same distance to the target date are in the same range from normal value, the data measured at an earlier date will be used for summary tables.

For ECG parameters in Part 1, the analysis window for each time point may be set up depending on actual data in individual data monitoring meeting, if necessary.

The visit window is applied for safety assessment item which is scheduled at each visit. The window is summarized following tables.

For every 2 weeks regimen in Part 1;

Analysis visit	Target Day	Visit Window	
		Start Day of Visit Window	End Day of Visit Window
Cycle 1 Day 8	Cycle 1 Day 1 + 7	Cycle 1 Day 1 + 7	Cycle 1 Day 1 + 7
Cycle 1 Day 15	Cycle 1 Day 1 + 14	Cycle 1 Day 1 + 14	Cycle 1 Day 1 + 14
Cycle 1 Day 22	Cycle 1 Day 1 + 21	Cycle 1 Day 1 + 21	Cycle 1 Day 1 + 21
Cycle 2 Day 8	Cycle 2 Day 1 + 7	Cycle 2 Day 1 + 6	Cycle 2 Day 1 + 8
Cycle 2 Day 15	Cycle 2 Day 1 + 14	Cycle 2 Day 1 + 13	Cycle 2 Day 1 + 15
Cycle 2 Day 22	Cycle 2 Day 1 + 21	Cycle 2 Day 1 + 20	Cycle 2 Day 1 + 22
Cycle n Day 8 (n ≥ 3)	Cycle n Day 1 + 7	Cycle n Day 1 + 4	Cycle n Day 1 + 10
Cycle n Day 15 (n ≥ 3)	Cycle n Day 1 + 14	Cycle n Day 1 + 12	Cycle n Day 1 + 16
Cycle n Day 22 (n ≥ 3)	Cycle n Day 1 + 21	Cycle n Day 1 + 18	Cycle n Day 1 + 24
Discontinuation*	Date of discontinuation	Date of discontinuation - 7	Date of discontinuation + 7
Final observation*	Date of last dose + 30	Date of last dose	Date of last dose + 37

*: the data for the analysis visit can be duplicate of other time point data

For every 3 weeks regimen in Part 1;

Analysis visit	Target Day	Visit Window	
		Start Day of Visit Window	End Day of Visit Window
Cycle 1 Day 8	Cycle 1 Day 1 + 7	Cycle 1 Day 1 + 6	Cycle 1 Day 1 + 8
Cycle 1 Day 15	Cycle 1 Day 1 + 14	Cycle 1 Day 1 + 13	Cycle 1 Day 1 + 15
Cycle 2 Day 8	Cycle 2 Day 1 + 7	Cycle 2 Day 1 + 6	Cycle 2 Day 1 + 8
Cycle 2 Day 15	Cycle 2 Day 1 + 14	Cycle 2 Day 1 + 13	Cycle 2 Day 1 + 15
Cycle n Day 8 (n ≥ 3)	Cycle n Day 1 + 7	Cycle n Day 1 + 4	Cycle n Day 1 + 10
Cycle n Day 15 (n ≥ 3)	Cycle n Day 1 + 14	Cycle n Day 1 + 11	Cycle n Day 1 + 17
Discontinuation*	Date of discontinuation	Date of discontinuation - 7	Date of discontinuation + 7
Final observation*	Date of last dose + 30	Date of last dose	Date of last dose + 37

*: the data for the analysis visit can be duplicate of other time point data

8.4 Pharmacokinetic Data Handling

8.4.1 Lower Limit of Quantification of E7130 Plasma Concentration

The LLOQ of E7130 concentration in plasma, urine, and feces are 0.00200 ng/mL, 0.100 ng/mL, and 0.100 ng/g feces, respectively.

8.4.2 BLQ Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, BLQ values will be handled according to 302-104.00-MNL.

8.4.3 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.00-MNL.

8.4.4 BLQ Handling for Developing Figures of individual ECG parameter values – plasma Concentration of E7130

When developing figures of individual ECG parameter (QTcF or ΔQTcF) values-plasma concentration of E7130, BLQ values will be assigned to "zero".

8.4.5 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow 302-104.00-MNL.

8.4.6 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD and CV) will have 3 significant digits. For t_{max}, raw values are median are shown in fixed 2 decimal places.

Typical variable	Unit	N	Digit rule	Raw Minimum Maximum	Mean Median	SD	Geometric Mean	CV (%)
Plasma E7130 concentration	ng/mL	X	Significant digits	3	3	3	-	-
Urinary E7130 concentration	ng/mL	X	Significant digits	3	3	3	-	-
Fecal E7130 concentration	ng/g feces	X	Significant digits	3	3	3	-	-
C_{max}, C_{end}, C_{trough}	ng/mL	X	Significant digits	3	3	3	3	3

t_{max} [a]	h	X	Fixed decimal places	2	2	-	-	-
λ_z	1/h	X	Significant digits	3	3	3	3	3
$t_{1/2}$	h	X	Significant digits	3	3	3	3	3
$AUC_{(0-t)}$ $AUC_{(0-inf)}$	ng•h/mL	X	Significant digits	3	3	3	3	3
$\%AUC_{ex}$	%	X	Significant digits	3	-	-	-	-
CL	L/h/m^2	X	Significant digits	3	3	3	3	3
V_{ss}	L/m^2	X	Significant digits	3	3	3	3	3
MRT	h	X	Significant digits	3	3	3	3	3
A_e	µg	X	Significant digits	3	3	3	3	3
Fe	%	X	Significant digits	3	3	3	3	3
CL_R	L/h	X	Significant digits	3	3	3	3	3

a: Mean, SD, geometric mean and CV will not be calculated for t_{max}.

CV(%)= sqrt(exp[SD^2 of log transformed data]-1)×100

NOTE: The following parameters are reported in the CSR, but appear in Listings only. They are important information to confirm that individual $t_{1/2}$ and its related parameters such as $AUC_{(0-inf)}$ are appropriately derived and allow those PK parameters to be reproduced when necessary.

a) Time points used for estimation of λ_z (lower and upper)
b) Number of the time points used for λ_z
c) Adjusted regression coefficient (R^2adj)
d) Percentage of $AUC_{(0-inf)}$ obtained by extrapolation (%AUCex)

In Listings, a) are shown in same digits as actual sampling time after dosing used for calculation of PK parameters. For b), integer number is used in Listings. For c) and d), significant 3 digits are used in Listings.

9 PROGRAMMING SPECIFICATIONS

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

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS (version 9.3 or later) or WinNonlin (Professional version 6.2.1 or later). As necessary, other validated statistical software will also be used.

Validation method and analysis conductor

All statistical analyses apart from PK parameter calculation will be conducted by a contract research organization, using validated standard programs or double programming. For analyses needed in data review, single programming will be used. PK parameter calculation will be conducted by Eisai.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

- Bartholomew, D. Isotonic inference. In: Samuel K, Norman LJ, editors. Encyclopedia of Statistical Science volume 4, New York: Wiley-Interscience. 1983;260-5.
- Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7:653-63.
- Ji Y, Wang, S. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the3 + 3 Design for Practical Phase I Trials. J Clin Oncol. 2013;31:1785-91.
- FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007 [internet; cited 3 March 2011] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

13 APPENDICES

13.1 National Institute for Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

National Cancer Institute (NCI) Cancer therapy evaluation program Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 May 2009 (v4.03 June 2010) is available online at:

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

CTCAE grades for selected laboratory parameters are listed in the table below, where ULN is the upper limit of normal and LLN is the lower limit of normal.

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology					
Hemoglobin (low)	100 - <LLN (g/L)	80 - <100 (g/L)	<80 (g/L)	__	Death
Hemoglobin (high)	Increase in >0 - 20 g/L above ULN (ie., Increase in >0 - 2 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >20 - 40 g/L above ULN (ie., Increase in >2 - 4 gm/dL above ULN) or above baseline if baseline is above ULN	Increase in >40 g/L above ULN (ie., Increase in >4 gm/dL above ULN) or above baseline if baseline is above ULN	__	__
Platelet Count (PLT) (low)	75 - <LLN (x 10^9/L)	50 - <75 (x 10^9/L)	25 - <50 (x 10^9/L)	<25 (x 10^9/L)	__
White Blood Cell Count (WBC) (low)	3 - <LLN (x 10^9/L)	2 - <3 (x 10^9/L)	1 - <2 (x 10^9/L)	<1 (x 10^9/L)	__
White Blood Cell Count (WBC) (high)	__	__	>100 x 10^9/L (ie., >100,000/mm^3)	__	Death
Lymphocytes (low)	0.8 - <LLN (x 10^9/L)	0.5 - <0.8 (x 10^9/L)	0.2 - <0.5 (x 10^9/L)	<0.2 (x 10^9/L)	__
Lymphocytes (high)	__	>4 - 20 (x 10^9/L) (ie., >4,000 - 20,000/mm^3)	>20 (x 10^9/L) (ie., > 20,000/mm^3)	__	__
Neutrophils (low)	1.5 - <LLN (x 10^9/L)	1 - <1.5 (x 10^9/L)	0.5 - <1 (x 10^9/L)	<0.5 (x 10^9/L)	__

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blood Coagulation					
INR (high)	>1 - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN	__	__
Blood Chemistry					
Albumin (low)	30 - <LLN (g/L)	20 - <30 (g/L)	<20 (g/L)	__	Death
Alkaline Phosphatase (ALP) (high)	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
ALT (SGPT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
AST (SGOT) (high)	>ULN - 3 x ULN	>3 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	__
Total Bilirubin (high)	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	__
Calcium, serum-low (hypocalcemia)	2.0 - <LLN (mmol/L) (ie., 8.0 mg/dL - <LLN) *	1.75 - <2 (mmol/L) (ie., 7.0 - <8.0 mg/dL) *	1.5 - <1.75 (mmol/L) (ie., 6.0 - <7.0 mg/dL) *	<1.5 (mmol/L) (ie., <6.0 mg/dL) *	Death
Calcium, serum-high (hypercalcemia)	>ULN – 2.9 (mmol/L) (ie., >ULN – 11.5 mg/dL) *	>2.9 – 3.1 (mmol/L) (ie., >11.5 – 12.5 mg/dL) *	>3.1 – 3.4 (mmol/L) (ie., >12.5 – 13.5 mg/dL) *	>3.4 (mmol/L) (ie., >13.5 mg/dL) *	Death
Cholesterol (high)	>ULN -7.75 mmol/L	>7.75 -10.34 mmol/L	>10.34 -12.92 mmol/L	>12.92 mmol/L	__
CPK (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	__
Creatinine (high)	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN	>6.0 x ULN	__
GGT (gamma-glutamyltransferase) (high)	>ULN – 2.5 x ULN	>2.5 x ULN – 5.0 x ULN	>5.0 x ULN – 20.0 x ULN	>20.0 x ULN	__
Glucose, serum-low (hypoglycemia)	3 - <LLN (mmol/L)	2.2 - <3 (mmol/L)	1.7 - <2.2 (mmol/L)	<1.7 (mmol/L)	Death
Glucose, serum-high (hyperglycemia)	ULN – 8.9 (mmol/L)	>8.9 – 13.9 (mmol/L)	>13.9 – 27.8 (mmol/L)	>27.8 (mmol/L)	Death

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Lipase (high)	>ULN – 1.5 x ULN	>1.5 – 2.0 x ULN	>2.0 – 5.0 x ULN	>5.0 x ULN	--
Magnesium (low)	<LLN – 0.5 (mmol/L)	<0.5 – 0.4 (mmol/L)	<0.4 – 0.3 (mmol/L)	<0.3 (mmol/L)	Death
Magnesium (high)	>ULN – 1.23 (mmol/L)	--	>1.23 – 3.30 (mmol/L)	>3.30 (mmol/L)	Death
Triglyceride (hypertriglyceridemia) (high)	1.71 – 3.42 (mmol/L)	>3.42 – 5.7 (mmol/L)	>5.7 – 11.4 (mmol/L)	>11.4 (mmol/L)	Death
Phosphate, serum-low (hypophosphatemia)	0.8 - <LLN (mmol/L)	0.6 - <0.8 (mmol/L)	0.3 - <0.6 (mmol/L)	<0.3 (mmol/L)	Death
Potassium, serum-low (hypokalemia)	3.0 - <LLN (mmol/L)	--	2.5 - <3.0 (mmol/L)	<2.5 (mmol/L)	Death
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 (mmol/L)	>5.5 – 6.0 (mmol/L)	>6.0 – 7.0 (mmol/L)	>7.0 (mmol/L)	Death
Uric Acid (hyperuricemia) (high)	>ULN – 590 (umol/L)	--	--	>590 (umol/L)	--
Sodium, serum-low (hyponatremia)	130 - <LLN (mmol/L)	--	120 - <130 (mmol/L)	<120 (mmol/L)	Death
Sodium, serum-high (hypernatremia)	>ULN - 150 (mmol/L)	>150 - 155 (mmol/L)	>155 - 160 (mmol/L)	>160 (mmol/L)	Death
Urinalysis					
Proteinuria (high)	1+ proteinuria; urinary protein <1.0 g/24 hrs	≥2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs	urinary protein >=3.5 g/24 hrs	--	--

* Corrected serum calcium by albumin should be referred. If serum albumin is <4.0 g/dL, the corrected calcium will be calculated using the following formula: Corrected calcium (mg/dL) = Total calcium (mg/dL) – 0.8 x [Albumin (g/dL) – 4]

13.2 Dose Assignment Using Modified Toxicity Probability Interval (mTPI) Design

Number of Subjects With DLT	Number of Evaluable Subjects at The Current Dose																		
	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
0	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
1	**S**	**S**	**S**	**S**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
2	**D**	**D**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]	**S**	**S**	**S**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
3	**D,U**	**D,U**	**D,U**	**D**	**S**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**	**S**	**S**	**E**	**E**
4		**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]
5			**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D**	**S**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]	**S**[a]
6				**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D**	**S**	**S**	**S**	**S**	**S**[a]	**S**[a]	**S**[a]
7					**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**S**	**S**	**S**	**S**	**S**
8						**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**S**	**S**
≥9							**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**	**D,U**

E = Escalate to the next higher dose, S = Stay at the current dose, D = De-escalate to the next lower dose[b], U = Current dose is unacceptably toxic (ie, Do not re-enter the current dose)

Target DLT rate at MTD = 25%, its equivalence toxicity interval = 20 to 30%

Display for more than 21 subjects at the current dose is omitted.

a: Early MTD determination and initiation of exploring OBD candidate may be considered.

b: If a 100% or 50% dose escalation resulted in "D", then an intermediate dose level between pre- and post-dose escalation would be evaluated in the next cohort.

A beta distribution of Beta (1, 1) based on a beta/binomial hierarchic model was used for the prior distribution. When a posterior probability of being the target DLT rate of 25% is >95% at particular dose level, the relevant dose assignment is defined as "U".

If the Bayesian predictive probability that future dose assignments will be S is 80% or greater when 9 further subjects are added to a particular dose level, early MTD determination may be considered.

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