1 TITLE PAGE



Clinical Study Protocol

Study Protocol Number:	E7130-J081-101	
Study Protocol Title:	A phase 1 study of E7130 in subjects with solid tumor	
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-Ku, Tokyo 112-8088, Japan	
Sponsor's Investigational Product Name:	E7130	
Indication:	Solid tumor	
Phase:	Phase 1	
Approval Date:	V1.0	16 Nov 2017 (Original Protocol)
	V2.0	07 Dec 2017 (Amendment 01)
	V3.0	26 Nov 2018 (Amendment 02)
	V4.0	15 Apr 2019 (Amendment 03)
	V5.0	13 Nov 2019 (Amendment 04)
	V6.0	15 Jun 2021 (Amendment 05)
	V7.0	17 Dec 2021 (Amendment 06)
	V8.0	11 Mar 2022 (Amendment 07)
	V9.0	05 Oct 2022 (Amendment 08)
	V10.0	25 Sep 2023 (Amendment 09)
	V11.0	20 Dec 2024 (Amendment 10)
GCP Statement:	This study is to be performed in full compliance with all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.	
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in	

writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7130

Name of Active Ingredient: To be determined.

Study Protocol Title

A phase 1 study of E7130 in subjects with solid tumor

Site(s)

Study location (country): Japan

Study centers: One to 2 sites for Part 1, multiple sites (9 to 11 sites) for Part 2

Study Period and Phase of Development

Approximately 101 months, Phase 1

Objectives

Primary Objective

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

Secondary objectives

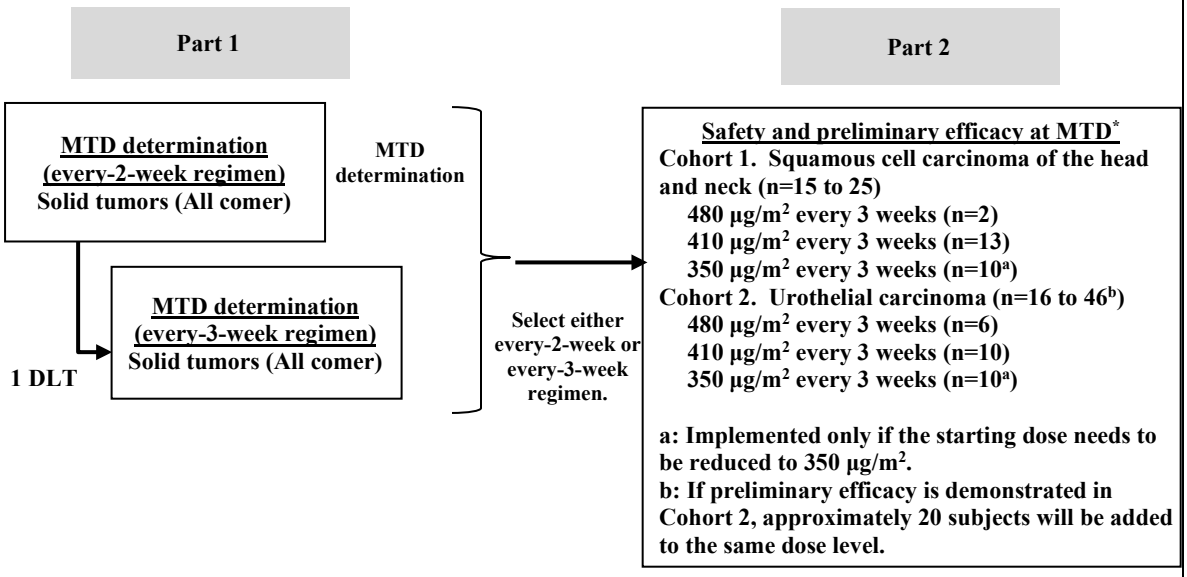
- To determine the maximally tolerated dose (MTD) of E7130 (only in Part 1).
- To evaluate the pharmacokinetics (PK) of E7130.
- To determine the recommended dose (RD) of E7130 for future studies.
- To evaluate objective response rate (ORR), disease control rate (DCR) and clinical benefit rate (CBR).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

CCI [redacted]

Study Design

This is a Phase 1 study of E7130 in subjects with solid tumors. This study will be conducted in 2 parts (Part 1 and Part 2). Part 1 will assess dose-limiting toxicity (DLT) when E7130 is administered to subjects with solid tumors and determine the MTD. Efficacy, safety, PK, and biomarkers will be evaluated to select the regimen and dose to be used in Part 2 from either of the every-2-week and every-3-week regimens that were evaluated in Part 1 (The regimen and dose to be used in Part 2 had been determined to be the MTD of 480 $\mu g/m^2$ every 3 weeks [added in the protocol version 6]) (Based on the safety results of 480 $\mu g/m^2$ [every-3-week regimen] in the first 8 subjects in Part 2, the regimen and dose to be used in Part 2 were changed to 410 $\mu g/m^2$ every 3 weeks). In addition, the regimen and dose used in Part 2 may be reduced to 350 $\mu g/m^2$ every 3 weeks based on the safety results of the first 10 subjects (total of Cohorts 1 and 2) receiving 410 $\mu g/m^2$ every 3 weeks. If Grade 3 or higher peripheral sensory neuropathy and/or Grade 3 or higher ileus attributable to neuropathy occurred in ≥3 of the first 10 subjects by Day 1 of Cycle 3

(C3D1), the dose should be reduced to 350 μg/m^2. Furthermore, a dose reduction to 350 μg/m^2 may be decided in consultation between the sponsor and the investigator based on the overall safety up to C3D1. In order to ensure the safety of subjects, the conditions of subjects will be checked more frequently than the specified schedule as necessary, and adverse events (AEs) will be evaluated as needed. If complete response (CR) or partial response (PR) is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2, approximately 20 subjects will be added to that dose level. CR and PR require confirmation by the subsequent response assessment at 4 weeks or later [added in the protocol version 8]). Part 2 will consist of 2 cohorts to further characterize the tolerability and safety of E7130 and to evaluate the preliminary efficacy of E7130 at the MTD in subjects with squamous cell carcinoma of the head and neck (SCCHN) in Cohort 1 and urothelial carcinoma (UC) in Cohort 2. The RD of E7130 for future studies will be estimated based on the data from Part 1 and Part 2.



* The regimen and dose to be used in Part 2 had been determined to be the MTD of 480 μg/m^2 every 3 weeks [added in the protocol version 6]. Based on the safety results of 480 μg/m^2 (every-3-week regimen) in the first 8 subjects in Part 2, the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks. In addition, the regimen and dose used in Part 2 may be reduced to 350 μg/m^2 every 3 weeks based on the safety results of the first 10 subjects (total of Cohorts 1 and 2) receiving 410 μg/m^2 every 3 weeks. If Grade 3 or higher peripheral sensory neuropathy and/or Grade 3 or higher ileus attributable to neuropathy occurred in ≥3 of the first 10 subjects by C3D1, the dose should be reduced to 350 μg/m^2. Furthermore, a dose reduction to 350 μg/m^2 may be decided in consultation between the sponsor and the investigator based on the overall safety up to C3D1. In order to ensure the safety of each subject, the conditions of subjects will be checked more frequently than the specified schedule as necessary, and AEs will be evaluated as needed. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2, approximately 20 subjects will be added to that dose level. CR and PR require confirmation by the subsequent response assessment at 4 weeks or later [added in the protocol version 8].

Study Design Overview

1. Part 1: Part 1 will be conducted in subjects with solid tumors. Part 1 will consist of a Pretreatment Phase, Treatment Phase, and Follow-up Phase. 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 the every-2-week and every-3-week regimens and subsequent cycles for sequence treatment. First, DLT assessment will be initiated to determine the MTD of the every-2-week regimen. Once the first DLT with the every-2-week regimen occurred, DLT assessment will be started to select the MTD for the every-3-week regimen at a one dose lower (–1) than the dose where the first DLT with the every-2-week regimen was observed. The DLT assessment with the every-2-week and every-3-week regimens will be performed in parallel. Based on the results of DLT assessment including a PK profile of the every-2-week regimen, DLT assessment with the every-3-week regimen may be started before the first DLT with the every-2-week regimen is observed. For Cycle 1 and onward, each cycle is 28 days long for the every-2-week regimen and 21 days long for the every-3-week regimen. In Cycle 1 and onwards, subjects will be administered E7130 every 2 weeks (Days 1 and 15 of each cycle) or every 3 weeks (Day 1 of each cycle) until they meet any of the criteria in the "Criteria for discontinuation." Considering visit schedule and safety, in the dose escalation cohort, subjects will be admitted to the hospital from the day before Cycle 1 Day 1 (C1D1) to Cycle 2 Day 2 (C2D2) (for safety assurance, up to the end of Cycle 1 [DLT evaluation period]) as a rule. The Follow-up Phase will consist of the examination at study discontinuation and the last observation visit.

Dose escalation and 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, the MTD of E7130 for the every-2-week regimen will be determined in the following manner. The initial dose level of E7130 for the every-2-week regimen will be 25 μg/m^2, and the first cohort would enroll 3 subjects for DLT evaluation. In the first cohort only, initial administration of E7130 in the second subject must be started on or after the 29th day after C1D1 of the first subject. If drug-related Grade 2 or higher toxicity excluding clinically insignificant events occurred 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 excluding clinically insignificant events is NOT identified in the initial cohort, DLT will be evaluated at successive dose levels in a single subject each until such a toxicity occurs. If such a toxicity is observed, the cohort will be expanded to enroll a total of 3 subjects.

After that, each subject will be assigned to a dose of E7130 in accordance with the rules of the mTPI design based on a target DLT rate of 25% in this study 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 the "Decision Rule for Dose Assignment" below.

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,
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 may be considered.

The DLT assessment and the next dose level will be selected based on the results of the 3-subject cohort using the mTPI design. Based on the number of subjects developing DLT(s) during the DLT assessment period at each dose level, dose assignment (escalate, stay, de-escalate) for the next 3 subjects will be determined according to the above table. However, the dose assignment for the next 3 subjects can be decided by taking into consideration the treatment compliance in Cycle 2, etc., in addition to the number of subjects who developed DLTs. When 1 subject has already been evaluated at the next dose level, 2 subjects will be enrolled, and dose assignment will be determined based on the results from the 3 subjects. In the case where 4 or more subjects were enrolled and evaluated in a cohort, dose assignment will be decided based on the results from all the subjects at the dose. The next cohort at the dose level will enroll and assess 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 assessed as the another cohort. At the new dose level where 3 subjects (except for the initial dosing cohort of the every-2-week regimen) are enrolled, the second subject should start to receive the initial administration of E7130 on or after the following day after the first subject is observed on C1D1. Subjects who are not evaluable for DLT (for example, those 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 each (except for initial dosing cohort), the MTD for the every-2-week regimen will be determined. However, the maximum number of cohorts may be adjusted as required. In addition, early determination of MTD may be considered if the probability of future subjects also being allocated to that dose is expected to be high enough. The details of this design are described in the Section "Statistical Methods."

The dose escalation range is 100% until development of drug-related Grade 2 toxicity in 1 subject. The range would be switched to 50% after development of such a toxicity. When

drug-related Grade 2 in ≥2 subjects during study and/or Grade 3 or higher toxicity in ≥1 subject occurred, the dose escalation range would be switched to 33%. The dose escalation ranges are summarized in the table below. If a 100% or 50% dose escalation resulted in "De-escalate" in the above table, then an intermediate dose level between pre-dose escalation and post-one would be evaluated in the next cohort. When escalating to the next dose level according to the mTPI design, and if there is a higher dose level that has been tested previously, the higher dose recently studied will be assessed in the next cohort without applying the "Method for deciding the dose of the next cohort." However, doses other than the abovementioned ones may be evaluated after consultation among the investigator, sponsor, and medical expert.

Method for deciding the dose of the next cohort

Dose escalation for the next cohort (%)	Drug-related toxicity that developed during Cycle 1
100	Grade ≤1 only
50	Grade 2 in 1 subject
33	Grade 2 in ≥2 subjects during study and/or Grade ≥3 in ≥1 subject

(*) Excluding clinically insignificant events (eg, alopecia or abnormal laboratory parameters not requiring medical treatment) as this toxicity for deciding the dose of the next cohort.

Transition to the next cohort and dose assignment, dose escalation range, transition timing of DLT assessment for the every-3-week regimen, initial dose of the every-3-week regimen, and transition timing to Part 2 will be decided based on the discussions among the investigator, sponsor, and medical expert. If necessary, the suggestions from independent medical advisors will be sought for this purpose.

A dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate for each dose will be defined as the MTD of the every-2-week regimen. Once the MTD is selected in accordance with this procedure, the MTD will be finally determined while taking toxicity data up to Cycle 2 into account. After the first DLT with the every-2-week regimen is identified, DLT assessment will be initiated to determine the MTD of the every-3-week regimen at a one lower dose (–1) than the dose where the first DLT with the every-2-week regimen was identified. Based on the results of DLT assessment including the PK profile of the every-2-week regimen, DLT assessment of the every-3-week regimen may be started before the first DLT with the every-2-week regimen is observed. The initial dose level of E7130 for the every-3-week regimen will be decided based on the safety profile of the every-2-week regimen, and the first cohort would enroll 3 subjects for DLT evaluation.

The dose assignment rules for the every-3-week regimen are also determined by mTPI method described above. To determine dose assignment for the every-3-week regimen, the DLT evaluation results at the same dose level in the every-2-week regimen will not be pooled. When DLT evaluation is completed in 5 cohorts being composed of 3 subjects, the MTD for the every-3-week regimen will be selected in the same manner as that for the every-2-week regimen. However, the maximum number of cohorts may be adjusted as required. The dose escalation range for every-3-week dose finding will be decided according to the "Method for deciding the dose of the next cohort," and the maximum range is 50%.

If there are subjects who could not complete infusion of E7130 on C1D1 and C1D15 (every-2-week regimen only) or the DLT assessment of a 28-day (every-2week regimen) or 21-day (every-3-week regimen) period following the first dose of E7130 because of any reasons except DLTs, the sponsor should discuss whether the subjects should be included in the DLT Analysis Set with the investigator, medical expert and if necessary, independent medical advisors. Based on the discussion, the sponsor can also replace DLT evaluable subjects by enrolling additional subjects.

In addition, transition to the next dose levels and dose escalation range will be decided while taking into account of the safety data of those subjects who were excluded from the DLT Analysis Set as well.

Determination of MTD regimen to be used in Part2

The dosing regimen to be used in Part 2 will be selected after the MTDs of the every-2-week and every-3-week regimens are determined. However, based on preclinical and clinical findings (including safety and tolerability, PK, efficacy, and biomarker findings from Part 1), the dosing regimen can also be defined after determination of the MTD of either every-2-week or every-3-week regimen.

[Added in the protocol version 6]

The dose regimen to be used in Part 2 was chosen to be the every-3-week regimen (MTD 480 μg/m^2).

2. Part 2: Part 2 will consist of 2 cohorts, and the MTD of the dosing regimen selected in Part 1 will be used (The regimen and dose to be used in Part 2 had been determined to be the MTD of 480 μg/m^2 every 3 weeks [added in the protocol version 6]) (Based on the safety results of 480 μg/m^2 [every-3-week regimen] in the first 8 subjects in Part 2, the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks). In addition, the regimen and dose used in Part 2 may be reduced to 350 μg/m^2 every 3 weeks based on the safety results of the first 10 subjects (total of Cohorts 1 and 2) receiving 410 μg/m^2 every 3 weeks. If Grade 3 or higher peripheral sensory neuropathy and/or Grade 3 or higher ileus attributable to neuropathy occurred in ≥3 of the first 10 subjects by C3D1, the dose should be reduced to 350 μg/m^2. Furthermore, a dose reduction to 350 μg/m^2 may be decided in consultation between the sponsor and the investigator based on the overall safety up to C3D1. In order to ensure the safety of each subject, the conditions of subjects will be checked more frequently than the specified schedule as necessary, and AEs will be evaluated as needed. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2, approximately 20 subjects will be added to that dose level. CR and PR require confirmation by the subsequent response assessment at 4 weeks or later [added in the protocol version 8]). Enrollment of subjects in each cohort will occur in parallel. Cohort 1 (SCCHN) will consist of approximately 15 to 25 subjects, and Cohort 2 (UC) will consist of approximately 16 to 46 subjects.
Part 2 will consist of a Pretreatment Phase, Treatment Phase, and 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 21 days (every-3-week regimen) in duration, and administration of E7130 every 3 weeks will continue until subjects meet any of the criteria in the "Criteria for discontinuation." The Follow-up Phase will consist of the examination at study discontinuation, last observation, and follow-up for OS. In the follow-up for OS, the subjects' survival and post-anti-cancer treatment after

discontinuation of treatment with E7130 will be followed every 6 months (approximate) and if requested by the sponsor up to 18 months after enrollment of the last subject.

3. RD determination: The RD will be selected based on the MTD, efficacy, safety, PK profile and biomarker data in Part 1 and Part 2.

Number of Subjects

Part 1: Approximately 40 subjects.

Part 2: Approximately 30 to 50 subjects (If the starting dose is reduced to 350 μg/m^2, approximately 20 additional subjects may be enrolled.)

Cohort 1. SCCHN (approximately 15 to 25 subjects)

Cohort 2. UC (approximately 16 to 46 subjects)

Inclusion Criteria

1. Subjects who have provided voluntary written consent for participation in this clinical study.
2. Subjects to whom the rules for complying with this clinical study have been adequately explained, and who intend to and can comply with these rules.
3. Subjects aged ≥20 years at the time of informed consent.
4. Part 1: Subjects with a histological and/or cytological diagnosis of solid tumor who failed standard therapies, or for which no appropriate treatment is available.
   Part 2, Cohort 1: Subjects with a histologically documented diagnosis of unresectable SCCHN who previously received at least 1 but no more than 3 regimens of prior systemic therapy for advanced or metastatic disease.
   Part 2, Cohort 2: Subjects with a histologically or cytologically documented diagnosis of unresectable UC of the bladder, urethra, ureter, or renal pelvis who previously received systemic therapy with a platinum and immune checkpoint inhibitor. Systemic therapies for advanced or metastatic disease should be no more than 3 regimens.
5. Subjects with adequate function of major organs.
   a. Hemoglobin ≥9.0 g/dL.
   b. Neutrophil count ≥1.5×10^3/μL.
   c. Platelet count ≥10×10^4/μL.
   d. Total bilirubin ≤1.5× upper limit of normal (ULN) in the facility.
   e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0×ULN in the facility.
      ≤5.0×ULN in the facility for subjects with liver metastases.
   f. Serum creatinine ≤1.5×ULN in the facility or creatinine clearance ≥30 mL/min for subjects with creatinine levels >1.5×ULN in the facility.
6. Subjects with Performance Status (PS) score of 0 to 1 established by Eastern Cooperative Oncology Group (ECOG).
7. Subjects who are expected to survive for 3 months or longer after starting administration of the investigational drug.
8. Washout period required from the end of prior treatment to the first administration of study drug will be as follows:
   a. Anticancer therapy

- Antibody and other study drugs: >4 weeks. (However, in the case where the half-life of other study drugs is known and 5× half-lives of that study drug is less than or equal to 4 weeks, subjects can be eligible after ≥5× half-lives of that study drug has passed.)
- Prior chemotherapy (except small-molecule targeted therapy), surgical therapy, radiation therapy: >3weeks.
- Endocrine therapy, immunotherapy (except antibody drug), small-molecule targeted therapy: >2 weeks.

b. Supportive therapies

- Blood/platelet transfusion, hematopoietic stimulating agent including granulocyte colony-stimulating factor (G-CSF) formulation: >2 weeks.

9. Subjects who agree to submit blood samples prior and during study treatment for PD markers.

Inclusion Criteria (Part 2 only)

10. Measurable disease meeting the following criteria:
    a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is serially measurable according to RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI).
    b. Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease to be deemed a target lesion.
11. (Cohort 1 only) Subjects with a lesion appropriate for biopsies before and after study infusion to be conducted as the biomarker assessment and who agreed to undergo biopsies at pre- and post-treatment, provide tumor tissues, and be included in PGx assessments.
12. (Cohort 1 only) Subjects with a primary lesion, local recurrent lesion, or cervical lymph node (≥2.0 cm) not affected by MRI susceptibility artifacts (eg, excluding bony or maxillary sinus involvement of the palate) that are suitable for imaging biomarker measurement. Lesions used for imaging biomarkers should be different from those for biopsies at pre- and post-treatment unless there is only one appropriate lesion.

Exclusion Criteria

1. Medical history of clinically significant cardiovascular impairment:
    a. Heart disease greater than or equal to New York Heart Association (NYHA) Class II.
    b. Unstable angina pectoris, myocardial infarction or stroke within 6 months before the first dose of study drug.
    c. Prolongation of corrected QT (QTc) interval to >480 msec (Fridericia method).
    d. Arrhythmia associated with hemodynamic instability within 6 months.
2. Serious concomitant systemic infection requiring medical treatment (including bacterial infection and fungal infection).
3. Subjects who test positive for human immunodeficiency virus (HIV antibody).
4. Active viral hepatitis (B or C)(*) as demonstrated by positive serology or requiring treatment.
    (*) HBsAg, anti-HBs/HBcAb and anti-HCV Ab test. Subject who are anti-HBs/HBcAb (+) with less than 20 IU/mL HBV-DNA are eligible.
    If HCV antibody is positive, HCV-RNA level will be measured. If negative, the subject can be enrolled.

5. Effusion requiring drainage. (Note: Subject whose symptom has been treated and stable for 2 weeks prior to the first administration of the study drug, is eligible.)
6. Subjects whose toxicity of previous treatment has not recovered to Grade 1 or lower (except for alopecia, and hemoglobin provided in Inclusion Criterion 5).
7. Other active malignancy (except for definitively treated non-invasive melanoma, basal or squamous cell carcinoma of the skin, carcinoma in-situ of the cervix, or carcinoma in situ of bladder) within the past 24 months prior to the first administration of the study drug. Other exclusions (eg, esophageal cancer completely removed by endoscopic treatment) may be considered after discussion and agreement with the sponsor.
8. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 3 days before the first dose of study drug (breastfeeding subjects are not eligible even if they discontinue breastfeeding).
9. Women of childbearing potential or man of impregnate potential who do not agree that both the subject and his/her partner will use a medically effective method for contraception (as below [Note 2)] during the study and after study drug discontinuation (male; 90 days, female; 60 days).[Note 1)]

   Note 1) The reporting period may be extended based on the half-life of E7130 calculated from this trial.

   Note 2) Condom,* contraceptive sponge,** foam,** jelly,** diaphragm,* intrauterine device (IUD),* or use of oral contraception* from at least 4 weeks before starting the study treatment

   (*Approved drugs or certified medical devices in Japan, **Non-approved drugs or certified medical devices in Japan).
10. Known intolerance to the study drug or any of the excipients.
11. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in the study.
12. Scheduled for surgery during the study.
13. Diagnosed with meningeal carcinomatosis.
14. Subjects with brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.

Exclusion Criteria (Part 2 only)

15. (Cohort 1 only) Subjects with a past or current history of medical conditions interfering with the imaging biomarker assessment of a cervical lesion (eg, cardiac pacemaker; ferromagnetic metal implant preventing safe imaging; obesity exceeding device limits; DCE/DW-MRI imaging not indicated; history of severe MRI contrast allergy; or renal impairment that would put the subject at risk of nephrogenic systemic fibrosis)

Study Treatment(s)

1. Part 1

Treatment (Part 1) In Part 1, E7130 will be administered as an every-2-week/3-week IV infusion. The study drug that will be used is 0.05 and 0.25 mg/mL vials.

Refer to the following volume of normal saline for preparation and infusion time, which depend on the magnitude of dose level. If no clinically significant AEs related to the study treatment occur during Cycle 1, the infusion time of the study drug can be halved in Cycle 2 and beyond (eg, when it is ≥60 minutes, ≥30 minutes). The investigator or subinvestigator should carefully monitor the condition of subjects after the modification.

Dose level	Infusion time
25 μg/m^2	≥5 min
>25 to 33 μg/m^2	≥7 min
>33 to 50 μg/m^2	≥10 min
>50 to 100 μg/m^2	≥15 min
>100 to 180 μg/m^2	≥30 min
>180 to 1800 μg/m^2	≥60 min
>1800 μg/m^2	≥120 min

(*): Refer to the manual provided by the sponsor concerning the dilution concentration, administration equipment (syringe, drip bag, etc.) according to the doses.

Dose interruption, skip and dose reduction for toxicity (Part 1)

1. Cycle 1

- If DLT occurs:
  E7130 will be interrupted/skipped immediately. When the investigator or subinvestigator judges it clinically appropriate, the next scheduled administration can be done at a reduced 1 dose level lower after toxicity is recovered to Grade ≤1 or baseline Grade as Cycle 2 Day 1 (C2D1). If the investigator or subinvestigator determines that no dose reduction is necessary, a decision will be made after prior consultation with the sponsor.
- If no DLT occurs:
  E7130 will not be interrupted/skipped as a rule until DLT is observed.
  When the investigator or subinvestigator judges it clinically appropriate during E7130 administration, E7130 can be interrupted or skipped and resumed at the same dose level at any time. The next scheduled administration can be done at the same dose level. Dose reduction cannot be permitted.

2. Cycle 2 or later

   The criteria for initiation and dose reduction of E7130 treatment, shown below, shall be followed when any E7130-related toxicity occurs.

Criteria for treatment initiation

E7130 will be administered when the subjects meet all of the following treatment criteria. For subjects who have not yet recovered from E7130-related toxicities to the following criteria, the next scheduled Cycle Day 1 may be postponed for up to 14 days for recovery from the toxicities. In addition, subjects who cannot receive the next scheduled Cycle Day 1 of E7130 due to holidays, public holidays etc., regardless of disease conditions, may receive the administration up to 7 days after the scheduled date. Further postponement if necessary will be determined in consultation with the sponsor.

- Neutrophil count ≥1.0×10^3/μL.

- Platelet count ≥7.5×10^4/μL.
- Non-hematological toxicity recovered to Grade 0 to 2 (excluding non-clinically significant laboratory abnormalities).

For subjects who cannot receive the study drug on Day 15 due to reasons such as E7130-related toxicities after Cycle 3 in the every-2-week regimen, the next scheduled day of Day 15 may be postponed for up to 7 days. When the scheduled administration date of Day 15 is postponed, E7130 administration on Day 1 of the next cycle must be NO SOONER than 14 days later from the actual administration day. In this case, the examination scheduled for Day 22 will be conducted 7 days after the actual administration day.

Criteria for dose reduction

If hematological toxicity or non-hematological toxicity of the same severity as that specified by the DLT criteria occurs, the subsequent doses of E7130 will be administered at a one level lower dose. The dose to be reduced will be determined by the investigator and sponsor based on the safety data available. If the investigator or subinvestigator determines that no dose reduction is necessary, a decision will be made after prior consultation with the sponsor. If a toxicity requiring to postpone study drug administration occurs, the next dose may be reduced by one level at the discretion of the investigator or subinvestigator. If a dose reduction is required for other reasons, a decision will be made in consultation with the sponsor. Once the dose is reduced, it cannot be increased at a later date.

2. Part 2 [Added in the protocol version 6]

Treatment (Part 2)

The study drug that will be used in Part 2 is the 0.25 mg/mL vial. E7130 will be administered at a dose of 480 μg/m^2 over 60 minutes (approximate) as an every-3-week IV infusion. E7130 will be administered at a dose of 410 μg/m^2 over 60 minutes (approximate) as an every-3-week IV infusion because the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks based on the safety results of 480 μg/m^2 obtained from the first 8 subjects in Part 2 since the protocol version 8. If no clinically significant AEs related to the study treatment occur during the first infusion of the study drug, the infusion time of the study drug can be changed to ≥30 minutes (approximate) in Cycle 2 and beyond. The investigator or subinvestigator should carefully monitor the condition of subjects if the infusion time is changed.

Dose interruption, skip and dose reduction for toxicity (Part 2)

The criteria for initiation and dose reduction of E7130 treatment, shown below, shall be followed when any E7130-related toxicity occurs.

Criteria for treatment initiation

E7130 will be administered when the subjects meet all of the following treatment criteria. For subjects who have not yet recovered from E7130 related toxicities to the following criteria, the next scheduled Cycle Day 1 may be postponed for recovery from the toxicities. For subjects who cannot receive the next scheduled Cycle Day 1 of E7130 due to other reasons such as holidays, public holidays etc., the next scheduled day of administration may be postponed. If treatment is postponed for >21 days, resumption should be discussed with the sponsor.

- Neutrophil count ≥1.0×10^3/μL.
- Platelet count ≥7.5×10^4/μL.
- Non-hematological toxicity recovered to Grade 0 to tolerable 2 (excluding non-clinically significant laboratory abnormalities).

Criteria for dose reduction

If any of the following toxicities occurs, the dose of E7130 will be administered at a one level lower dose. The dose should be reduced in the order of 480, 410, 350, and then 300 μg/m^2, and if a further dose reduction is necessary, the study should be discontinued as a rule. The dose should be reduced in the order of 410, 350, 300 and then 250 μg/m^2, and if a further dose reduction is required, the study should be discontinued as a rule because the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks based on the safety results of 480 μg/m^2 obtained from the first 8 subjects in Part 2 since the protocol version 8. If the starting dose is changed to 350 μg/m^2, the dose should be reduced in the order of 350, 300, 250 and then 200 μg/m^2, and if a further dose reduction is necessary, the study should be discontinued as a rule. If the investigator or subinvestigator determines that no dose reduction is necessary, a decision will be made after prior consultation with the sponsor. If a dose reduction is required for reasons other than the following toxicities, a decision will be made in consultation with the sponsor. Once the dose is reduced, it cannot be increased at a later date.

Starting dose: 410 μg/m^2→350 μg/m^2→300 μg/m^2→250 μg/m^2→ study discontinuation
Starting dose: 350 μg/m^2→300 μg/m^2→250 μg/m^2→200 μg/m^2→study discontinuation

Hematological toxicity	
- Grade 4 neutropenia persisting for ≥7 days[a] - Grade 3 – 4 febrile neutropenia[a] - Grade 4 thrombocytopenia or Grade 3 thrombocytopenia that requires blood transfusion - Grade 4 anemia, or anemia that requires blood transfusion	If the event occurred in the previous cycle, the dose should be reduced in the next cycle.
Non-hematological toxicity[b]:	
- Grade 4 - Grade 3 [c] - Intolerable Grade 2[d]	If the event occurred in the previous cycle, the dose should be reduced in the next cycle.
a: If these toxicities occur without prophylactic treatment, the next cycle dose may not be reduced with effective prophylactic treatment. Discuss and agree with the investigator, sponsor, and medical expert in advance. b: Excluding Grade3 - 4 laboratory abnormalities that are not clinically significant or recovered to Grade 0 - 2 without treatment c: Excluding any events which can be managed and controlled to Grade 2 or less by maximal medical management. d: Tolerability of Grade 2 events will be decided by the investigator or subinvestigator.	

Other Considerations

In the non-clinical study of E7130, there are no findings suggesting increased QT interval, but it has been reported that the QT interval increased after treatment with eribulin that is a synthetic analog of E7130. In this study, as shown in the Schedule of Procedures/Assessments (Table 13,

Table 14, Table 15), subjects will undergo electrocardiogram (ECG) and electrolyte tests (blood chemistry) before the first dose of the study drug as well as during the treatment with E7130 to carefully monitor the subjects' condition. Appropriate actions will be taken in case of any abnormal findings.

Duration of Treatment

E7130 will be continued until any of the following criteria for discontinuation is met.

Discontinuation Criteria by Subject

1. The subject refuses to continue participation in the study or wished to withdraw consent.
2. Major violations (eg, violations of the inclusion or exclusion criteria) are found after study enrollment, and they significantly affect the primary endpoint and subject safety.
3. The subject is unable to continue the study due to an AE in the opinion of the investigator or subinvestigator.
4. The subject becomes pregnant.
5. Progressive disease (When the investigator or subinvestigator judges clinical benefit of E7130 is maintained, it can be continued after discussion with the sponsor.)
6. When the dose of E7130 needs to be reduced to less than the starting dose (25 μg/m^2) in Part 1 and less than the minimum dose specified in Part 2 due to the development of a drug-related AE.
7. The investigator or subinvestigator thinks that discontinuation of the study is appropriate.

Concomitant Drug/Therapy

Prohibited Concomitant Drug/Therapy

1. Cycle 1 (Part 1 only)

   Treatments (*), changes in doses, and changes in drugs for the purpose to prevent DLT occurrence.

   (*) Prophylaxis treatment of nosocomial infection, acceptable treatment in DLT criteria or continuous treatment for complication is permitted ensuring that concomitant treatment should be kept to a minimum during this study. And unless the purpose to prevent DLT, G-CSF or equivalent may be used at the discretion of the investigator or subinvestigator in accordance with institutional or national guidelines.
2. From the start of the first dose of study drug to the time of study drug discontinuation (refer to Inclusion Criterion (8)).
   1. Treatments for malignant tumors other than E7130 such as surgery, chemotherapy, hormone therapy, and immunotherapy.
   2. Radiotherapy: However, palliative radiotherapy for bone metastasis of painful non-target lesions is allowed up to 2 lesions. Palliative radiotherapy is permitted only after completion of DLT assessment in Part 1.
   3. Other investigational drugs
3. Cycle 1 and 2 (Part 1 only)

   Inhibitor of P-glycoprotein (P-gp) (refer to the Attachment separately provided to each site)

Note: Concomitant use of drugs that inhibit P-gp should be avoided if possible from 14 days before C1D1 to 14 days after the last dose of study drug. If concomitant use of drugs that inhibit P-gp is

necessary during this period, the sponsor and medical expert should be contacted in advance (other than the prohibited concomitant period in Part 1 and Part 2).

Assessments

1. Efficacy Assessments

Tumor assessment (target lesion, non-target lesion, and presence or absence of new lesion) will be performed based on RECIST 1.1. Survival post-treatment will be a follow-up in Part 2 only.

Tumor assessments with CT for chest, CT or MRI of abdomen, pelvis, and any other known or suspected sites of disease at screening will be carried out. In Part 1, tumor assessments will be implemented at screening and every 6 weeks (±7 days) from C1D1 through week 24 (6, 12, 18, and 24 weeks), then every 12 weeks (±7 days) (eg, 36, 48, 60… weeks after C1D1) thereafter and at discontinuation, or in a timely manner if disease progression is clinically indicated. In Part 2, tumor assessments will be carried out at screening and every 6 weeks (±7 days) from C1D1, at discontinuation, or in a timely manner if disease progression is clinically indicated. Tumor assessments will be based on images acquired by the same imaging modality (eg, CT, MRI) and under the same operating conditions as the screening scan. In Part 2, subjects going off treatment without disease progression will also undergo tumor assessments every 6 weeks (±7 days) from C1D1 through Week 24 (6, 12, 18 and 24 weeks), then every 12 weeks (±7 days) thereafter until disease progression, initiation of another anticancer therapy, death, or cutoff date whichever comes first.

Subjects, except, for example, oral or IV contrast media are medically contraindicated, will undergo CT or MRI scans with contrast. Subjects with an allergy to contrast will be assessed with non-contrast CT for chest and MRI of abdomen and pelvis. Attenuation correction CT portions or ultrasonography will not be employed for tumor assessment. Low dose CT portions of a combined positron emission tomography (PET)-CT also will not be utilized for tumor assessment.

In Part 1, a brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at screening to assess potential central nervous system (CNS) disease and/or metastases. For subjects with previously treated eligible brain metastases, a brain scan must be conducted at all tumor assessment time points.

When bone lesions are suspected, bone scans (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) will be carried out at screening, every 24 weeks from C1D1 and as clinically indicated.

To ensure comparability throughout the study, it is critical that the same image modality, methodology and scan acquisition technique is applied, and contrast is consistently provided unless IV contrast becomes medically contraindicated during the course of treatment or the dose of contrast needs to be adjusted based on the subject's health status.

2. Pharmacokinetic Assessments

- Plasma and urine concentrations of E7130.
- CCI [redacted]

3. Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

If a mechanism of action of E7130 is made cleared in preclinical studies, additional biomarkers may be measured and analyzed. The objectives of biomarker measurement are the identification of factors that predict or determine clinical response to E7130, or that may be used to understand the pharmacology of E7130 in an individual. These analyses will be reported as a separate report.

1. Blood biomarker

Blood samples will be collected (mandatory in both Part 1 and Part 2). Biomarkers such as TGF-β1 and VEGF (but not limited to these) will be measured.

Part 1: Blood samples will be collected at predose, 24, 48, and 168 hours post-infusion on C1D1, at predose and 168 hours post-infusion on C1D15, predose on Day 1 of Cycle 2 to 3, and at discontinuation for the every-2-week regimen. For the every-3-week regimen, blood samples will be collected at predose, 24, 48, 168, and 336 hours post-infusion on C1D1, at predose on Day 1 of Cycle 2 to 3, and at discontinuation.

Part 2: Blood samples will be collected at predose on Day 1, on Days 8 and 15 of Cycle 1-2, predose on Day 1 and on Day 8 of Cycle 3-6, on Day 8 of Cycle 7 and thereafter, and at discontinuation.

2. Tumor tissue biomarker

Archival or biopsy tissues will be collected, and CD31, α-SMA positive CAF, etc., (but not limited to these) will be measured as biomarkers.

Part 1: Pre-treatment archival or biopsy tissues will be collected (The pre-treatment biopsy tissues may also serve as the pre-treatment archival tissues.).

Part 2: Biopsy tissues will be collected from all subjects as follows:

- Cohort 1 (SCCHN): Pre- and post-treatment (screening, C2D3 to C2D9) tissues will be collected from all subjects. This does not apply to cases where it is found difficult to perform biopsy at pre- and post-treatment after informed consent. Subjects must have consented to PGx. If a subject withdraws from the study prior to the post-treatment biopsy, a biopsy may be taken during the Follow-up Phase instead of a post-treatment biopsy. Prophylactic use of G-CSF for pre- and post-treatment biopsies should be considered. In addition, the sponsor may request the subjects to provide pre-treatment archival tumor tissues if any.
- Cohort 2 (UC): Pre-treatment archival or biopsy tissues will be collected from all subjects (The pre-treatment biopsy tissues may also serve as the pre-treatment archival tissues.). PGx is optional.

3. Imaging biomarkers (Part 2 only)

Part 2, Cohort 1 (SCCHN): DCE-MRI and DW-MRI will be performed at pre- and post-treatment (screening, C2D3 to C2D22) in all subjects. This does not apply to cases where it is found difficult to implement them after informed consent. Post-treatment assessments are recommended to be conducted between C2D8 and C2D15. If a subject is withdrawn from the study before DCE-MRI and DW-MRI at post-treatment, they can be performed during the Follow-up Phase instead of those at post-treatment. Biomarkers may include Ktrans, Ve, Kep, and ADC (but not limited to these). Refer to the separately provided manual for lesions suitable for the measurements. They will not be conducted in Cohort 2.

When there is only one lesion appropriate for DCE-MRI, DW-MRI and biopsy, and the same lesion will be used for the DCE-MRI and DW-MRI and biopsy, in principle, the biopsy should be implemented after DCE-MRI and DW-MRI at each time point, and DCE-MRI and DW-MRI should be carried out at least 3 weeks after the previous biopsy.

4. Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, and serious adverse events (SAEs) : Laboratory evaluation for hematology, blood chemistry, blood coagulation, and urinalysis, measurement of vital signs, arterial oxygen saturation, body weight and 12-lead ECGs, ECOG PS, and physical examinations at scheduled time points. In addition, DLTs will be assessed

to determine MTD. The severity of AEs will be graded according to the CTCAE v4.03. The following toxicities developed in Cycle 1 and the causal relationship with E7130 cannot be ruled out are regarded as "DLT." DLT determination will be agreed among the sponsor, investigators, and medical expert , and if necessary, an independent medical advisor.

1. DLT
   a. Febrile neutropenia
   b. Grade 4 neutropenia that persists for more than 7 days or that requires hematopoietic stimulating agents.
   c. Grade 4 thrombocytopenia or thrombocytopenia that requires platelet transfusion.
   d. Grade 4 anemia, or anemia that requires red blood cell transfusion.
   e. Any Grade 3 non-hematological toxicity with the exception of:
      - Abnormal clinical laboratory values with no clinical significance
      - Any events which can be managed and controlled to Grade 2 or less by maximal medical management.
   f. Any Grade 4 non-hematological toxicity
   g. (For the every-2-week regimen only) Development of any toxicity that is considered to be related to E7130 and where the dose was skipped on C1D15. However, when dose skip on C1D15 is required for reasons other than the following toxicities, this will not be deemed as a DLT. In this situation, the relevant subject will be excluded from assessments of DLT and new subjects will be added.
      - Neutrophil count $<1.0\times10^3/\mu L$.
      - Platelet count $<7.5\times10^4/\mu L$.
      - Intolerable Grade 2 or 3 non-hematological toxicity (excluding non-clinically significant laboratory abnormalities).
   h. (For the every-3-week regimen only) Development of any toxicity that is considered to be related to E7130 and where the dose at C2D1 needs to be postponed for over 14 days for recovery from the toxicities. However, when dose postponement on C2D1 is required for reasons other than toxicity, this will not be regarded as a DLT.
2. MTD determination

   A dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate for each dose will be defined as the MTD. Toxicity data up to Cycle 2 are taken into account to finally determine the MTD.
3. CCI [redacted]

Bioanalytical Methods

Concentrations of E7130 in plasma and urine will be quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) methodology using a previously validated assay, and validated or qualified methods will be used for blood biomarkers.

Statistical Methods

Statistical Design of Accelerated mTPI Method in Part 1

An accelerated mTPI design will be employed to determine the MTD of E7130. If drug-related Grade 2 or higher toxicity excluding clinically insignificant events is not observed in initial dosing cohort (3 subjects) of the every-2-week regimen, the dose will be escalated by single-subject DLT assessment in the following cohorts until drug-related Grade 2 or higher 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 3 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 3 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 the future dose level to be assigned, ie, dose escalation (E), staying at the current dose (S), or dose de-escalation (D), respectively.

This dose assignment rule minimizes the posterior expected penalty in the Bayes rule under a decision-theoretic framework with the equal prior expected penalties for E, S, and D. The entire dose assignment decision rule can be precalculated and presented.

The MTD will be determined when a prespecified maximum sample size, 7 or 5 cohorts being composed of 3 subjects for the every-2-week or every-3-week regimen, respectively (except for initial dosing cohort for the every-2-week 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, the MTD may be determined early.

The MTD is selected 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 up to Cycle 2 are taken into account to finally determine the 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) will be used to maintain monotonically increase of DLT rate with increasing dose level.

Study Endpoints

1. Primary Endpoints

   Primary objective is to evaluate the tolerability and safety profile of E7130 in subjects with solid tumors.

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

2. Secondary Endpoints

Secondary objectives are to determine the MTD of E7130, evaluate the PK of E7130 in plasma and urine, determine the RD for future studies, and assess the anti-tumor activity of E7130 in subjects with solid tumors. PFS and OS are also evaluated in Part 2 only.

- MTD determination: A dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate for each dose will be defined as the MTD. Toxicity data up to Cycle 2 are taken into account to finally determine the MTD.
- PK endpoints: PK parameters will be derived based on the plasma concentrations of E7130 using noncompartmental analysis (Part 1) and will include the following: 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 ($t_{½}$), total clearance (CL), and distribution volume (V_d). The amount of unchanged drug excreted in urine and renal clearance (CLR), if possible, will be derived in subjects who have urine samples in Part 1.
- RD determination: The RD is determined based on the MTD 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 are 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. 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). PFS censoring rules will be detailed in the statistical analysis plan (SAP). DOR is defined as the time from the first documented date of PR or CR 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.

3. Exploratory Endpoints

CCI [redacted]

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 Tumor Tissue and Imaging Biomarker Analysis Set is the group of subjects who received at least 1 dose of the study drug and had at least the pre-treatment tissues or data.

Efficacy Analyses

Efficacy analyses will be conducted based on the Efficacy Analysis Set. In Part 1, the results will be summarized by each dose group, separately by regimen (every 2 weeks/every 3 weeks). In Part 2, the results will be summarized by dose group in each cancer cohort.

Part 1: Based on the tumor assessments according to RECIST 1.1, BOR will be summarized. If a subject has a BOR of non-CR/non-PD, the subject's BOR will be grouped with the SD category. ORR, DCR, CBR and its corresponding exact 2-sided 95% confidence intervals will be calculated.

Part 2: Besides the similar analyses for the Part 1, 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). The percent changes from baseline over time in the sum of the diameters of target lesions will be presented using spider plot. PFS, DOR and OS will also be summarized and plotted over time by Kaplan-Meier method. To summarize PFS, DOR and OS, estimates of median, Q1, Q3 and probabilities at 12 weeks and adequate time points, but are not limited to, will be used.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetic Analyses

The PK analysis will be performed on the Pharmacokinetic Analysis Set. In Part 1, 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 (Part 1). Urine concentrations of E7130 will be analyzed to determine the PK parameters including the amount of unchanged drug excreted in urine and renal clearance (CLR), if possible, in subjects who have urine samples in Part 1. Plasma E7130 concentration data in Part 2 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.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

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

Tolerability/Safety Analyses

In Part 1, tolerability analysis results will be summarized by each dose group.Safety analysis results will be summarized by each dose group and for total dose group, separately by regimen (every 2 weeks/every 3 weeks). In Part 2, safety analysis results will be summarized by dose group in each cancer cohort, by cancer cohort, by dose group, and for whole subjects.

Tolerability analyses will be performed on the DLT Analysis Set. The number (percentage) of subjects with DLT will be summarized. Safety analyses will be performed on the Safety Analysis Set. The number (percentage) of subjects with treatment-emergent AEs (TEAEs) and treatment-emergent SAEs will be summarized by system organ class (SOC) and preferred term (PT).

Laboratory test results, vital signs, arterial oxygen saturation, weight, 12-lead ECGs, and ECOG PS including their changes from baseline will be summarized using descriptive statistics.

Pharmacokinetic-QT Interval Analyses

A plasma E7130 concentration-QTc analysis will be performed using 12-lead ECG data measured at the central laboratory.

Interim Analyses

No interim analysis is planned for this study. DLTs will be assessed sequentially according to the dose escalation schedule. In Part 2, analyses may be performed for each cohort. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2 in Part 2, approximately 20 subjects will be added to that dose level. CR and PR require confirmation by the subsequent response assessment at 4 weeks or later.

Details of addition of subjects to Cohort 2 in Part 2 are as follows: Beta (1, 1) as a prior distribution will be used to estimate the posterior probability. After 10 subjects who received the same dose in the UC cohort are followed for a sufficient period, the addition or discontinuation of subjects will be determined using the posterior probability. The probability cut-off will be 60% and the threshold ORR for the UC cohort will be 20%. The sample size at this dose level for the UC cohort will be expanded to a total of 30 subjects (20 additional subjects to the 10 subjects included in the interim evaluation in the expansion part) if the probability of the ORR exceeding 20% is ≥60%. That is, if ≥2 of 10 subjects respond, the cohort will be expanded. The cohort will not be expanded if there is <60% probability that the ORR is ≥20%.

Sample Size Rationale

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 the every-2-week regimen, if drug-related Grade 2 or higher toxicity is not observed in 3 subjects in the 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 the every-2-week 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 the every-3-week 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 in Part 2 will allow for further evaluation of safety and assessments of preliminary efficacy and biomarkers. The numbers of subjects were mainly based on the feasibility of enrollment. Cohort 1 will consist of 15 subjects with SCCHN, and Cohort 2 will include 16 subjects with UC. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2, approximately 20 subjects will be added to that dose level to further investigate safety and efficacy.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ALT	alanine aminotransferase
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BC	breast cancer
BOR	best overall response
β-hCG	beta-human chorionic gonadotropin
BUN	blood urea nitrogen
C#D#	Cycle # Day #
CAF	cancer associated fibroblast
CBR	clinical benefit rate
CL	total clearance
CL_{tot}	total clearance
C_{max}	maximum observed concentration
CR	complete response
CRC	coloreactal cancer
CRM	continual reassessment method
CRP	C-reactive protein
CT	computerized tomography
CYP	cytochrome P450
DCR	disease control rate
DE	dynamic contrast enhanced
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ER	estrogen receptor
GC	gastric cancer
GCP	Good Clinical Practice
G-CSF	granulocyte-colonystimulating factor
γ-GTP	gamma glutamyltransferase

Abbreviation	Term
HBc	hepatitis B core
HBs	hepatitis B surface
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
Her2	human epidermal growth factor receptor type2
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPV	human papillomavirus
IC_{50}	50% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	Identification
IUD	intrauterine device
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
LLT	lowest level term
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NE	not evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PAVA	Pooled Adjacent Violators Algorithm
PD	Pharmacodynamics
PD	progression of disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PK	Pharmacokinetics
PR	partial response

Abbreviation	Term
PR	progesterone receptor
PS	performance status
PT	preferred term
Q1	1st quartile
Q3	3rd quartile
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANKL	receptor activator of nuclear factor kappa-B ligand
RD	recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SOC	system organ class
SOP	standard operating procedure
STD_{10}	severely toxic dose in 10% of the animals
$t_{1/2}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
TEMAV	treatment emergent markedly abnormal laboratory value
TGF	transforming growth factor
t_{max}	time at which the highest drug concentration occurs
TME	tumor microenvironment
TNBC	triple negative breast cancer
TNM	tumor, nodes, metastasis
UPM	Unit Probability Mass
ULN	upper limit of normal
V_d	volume of distribution
$V_{d,ss}$	volume of distribution at steady state
VEGF	vascular endothelial growth factor

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an institutional review board (IRB) constituted and functioning in accordance with Good Clinical Practice (GCP). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB compliance with GCP regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB chairman must be sent to the head of the medical institution with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee. If the IRB decides to suspend or terminate the study, the head of the medical institution will immediately send the notice of study suspension or termination by the IRB to the sponsor.

Study progress is to be reported to IRBs annually (or as required) by the investigator via the head of the medical institution according to GCP. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the investigator, the head of the medical institution, and the relevant IRB via the head of the medical institution of any reportable adverse events (AEs) per GCP and local IRB standards of practice. Upon completion of the study, the investigator will provide the IRB and the sponsor via the head of the medical institution with a brief report of the outcome of the study.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki
- GCP

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator or subinvestigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB-approved ICF must be prepared in accordance with GCP and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The informed consent of submitting blood samples for blood biomarker and archival or biopsy tissues will be obtained. Blood samples for blood biomarker and archival or biopsy tissues will be collected from subjects who sign the consent. In Part 1, subjects who do not provide informed consent for pharmacogenomics (PGx) assessments using archival or biopsy tissues will also be eligible for the study. In Part 2, the informed consent for PGx assessments is mandatory.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsor at 1 to 2 investigational sites for Part 1 and multiple sites (9 to 11 sites) for Part 2, in Japan.

The name and telephone and fax numbers of the sponsor are listed in the Attachment separately provided to each site.

7 INTRODUCTION

7.1 E7130

E7130 is a novel microtubule inhibitor and a totally synthetic analog of norhalichondrin B (Hirata Y and Uemura D, 1986; Aicher TD, et al., 1992) isolated from the marine sponge (*Halichondria okadai* Kadota). Eribulin mesylate, described later, is a derivative of the "right half" fragment of halichondrin B (Hirata Y and Uemura D, 1986; Aicher TD, et al., 1992), while E7130 is a derivative of the total carbon skeleton of norhalichondrin B including the "left half" fragment.

Microtubules serve as an intracellular cytoskeleton framework and are dynamic structures that repeat elongation and shortening. Microtubules are involved in a wide variety of roles in the cell, including the cell shape, intracellular transport, cell motility, and cell division. These crucial functions make microtubules an important target for cancer therapy, and number of microtubule inhibitors were approved for clinical use. The microtubule-targeted drugs have diverse chemical structures and bind to different sites of tubulin, affecting microtubule dynamics in different ways (Jordan MA and Wilson L, 2004). Halichondrin compounds interact with the vinca domain, a region located at the interface of 2 tubulin heterodimers, in a different manner from other microtubule inhibitors (Bai R, et al., 2011; Doodhi H, et al., 2016). Its specific binding to the microtubule plus ends results in suppression of microtubule growth, but has no effect on the depolymerization (Jordan MA, et al., 2005; Smith JA, et al., 2010). Eribulin mesylate, a synthetic analog based on the right half of halichondrin B, is currently in clinical use for unresectable or relapsed breast cancer and malignant soft tissue tumor. Eribulin mesylate is reported to exert a potent antiproliferative activity against a variety of cancer cells (Towle MJ, et al., 2001) and also demonstrate an effect on tumor microenvironment in preclinical and clinical settings, so called vascular remodeling effect (Funahashi Y, et al., 2014; Ueda S, et al., 2016); it increased the microvessel density in tumor and decreased the hypoxic region that promoted the malignant phenotypes.

Preclinical researches demonstrated that E7130 showed an inhibitory action on the microtubule assembly and exhibited a potent antiproliferative activity against cancer cells. In addition, E7130 had unique effects on tumor microenvironment. E7130 showed the vascular remodeling effect in tumors as eribulin mesylate, and exhibited a more potent suppressive effect against the activated population of cancer associated fibroblasts (CAFs) than eribulin mesylate. CAFs are known to induce the tumor malignancy by secreting various cytokines and extracellular matrix proteins. As a summary, E7130 is expected to have a direct effect on cancer cells with the microtubule inhibition as well as unique effects on the tumor microenvironment.

7.2 Non-Clinical Studies of E7130

7.2.1 Pharmacodynamics

7.2.1.1 Primary Pharmacodynamics

E7130 showed inhibitory activity against the polymerization of tubulin in a concentration-dependent manner in the cell-free system. Antiproliferative assay using several cancer cells demonstrated E7130 exhibited potent antiproliferative activities with IC50 values below nanomolar, which were three- to eight-times potent than those of eribulin mesylate. MES-SA/Dx5-Rx1 uterine sarcoma cells, a P-glycoprotein (P-gp) expressing subline, showed 30-fold resistance to E7130 compared with the parental MES-SA cells while 1800-fold resistance was shown to eribulin mesylate. This result suggests that E7130 has lower possibility to become a substrate to P-gp than eribulin mesylate. E7130 exhibited significant and dose-dependent antitumor effects at doses from 45 μg/kg to 180 μg/kg against KPL-4 breast cancer and OSC-19 squamous cell carcinoma of the head and neck (SCCHN) xenografts in mice. In addition to direct antitumor activities, E7130 showed unique effects on the tumor microenvironment. E7130 increased the microvessel density in tumor and suppressed α-SMA positive population of CAFs in several xenograft models. We detected that these effects on tumor microenvironment contributed to an antitumor effect in the combinational setting such as the cetuximab combination. E7130 significantly enhanced delivery of cetuximab into tumor at 60 μg/kg and 180 μg/kg in the FaDu SCCHN xenograft model. The combinational treatment of E7130 with cetuximab significantly decreased α-SMA positive CAFs at 60 μg/kg and 180 μg/kg compared with cetuximab alone. The proliferative cancer cells were observed in the vicinity of α-SMA positive CAFs in the cetuximab alone group although remarkable decrease of the proliferative cells were shown in the E7130 plus cetuximab groups, suggesting that the E7130 suppressed cancer cell proliferation by reduction of α-SMA positive CAFs in tumor. We observed that E7130 exerted a clear antitumor activity with tumor regression at 60 μg/kg and 180 μg/kg in combination with cetuximab in a FaDu subcutaneous xenograft model. Moreover, the combination of E7130 at 90 μg/kg with cetuximab induced a clear tumor regression and a significant survival advantage in a HSC-2 orthotopic tongue transplantation model.

7.2.1.2 Safety Pharmacodynamics

E7130 was tested at 0.1 and 1.0 μmol/L in duplicate against a panel of 86 receptors, transporters and ion channels binding assays, all of important physiological function. Compound binding was calculated as a % inhibition of the binding of a radioactively labeled ligand specific for each target. As a results, E7130 showed no significant binding (>50% inhibition of radioligand specific binding) to all tested 86 targets at 0.1 and 1.0 μmol/L. Effect of E7130 on hERG potassium current was evaluated in hERG-CHO-K1 cells by a patch clamp system. No inhibitory effect on hERG potassium current was observed by E7130 up to 1.0 μmol/L. The effects of single intravenous administration of E7130 (1.5 or 15 μg/kg) on blood pressure, heart rate, electrocardiogram (ECG) parameters (PR interval, QRS time, and QTc interval), and body temperature were evaluated for 24 hours in 3 unanesthetized, unrestrained beagle dogs implanted with a telemetry transmitter. There was

no significant change in cardiovascular parameters at 1.5 or 15 μg/kg, and E7130 was not considered to have any effect on the cardiovascular system or body temperature up to 15 μg/kg. Due to the nature, conventional ECG monitoring will be conducted in the clinical development of E7130.

7.2.2 Pharmacokinetics/Metabolism

The pharmacokinetic profile of E7130 was evaluated after intravenous administration in rats and dogs. Rats showed linear pharmacokinetics within the dose range of 20 to 75 μg/kg. AUC increased dose-dependently, and total clearance (CL_{tot}, 2070 to 3440 mL/h/kg), distribution volume at steady state ($V_{d,ss}$, 881000 to 111000 mL/kg), and elimination half-life ($t_{1/2}$, 23.1 to 35.9 hours) were almost similar across the dose range. Dogs also showed linear pharmacokinetics within the dose range of 2 to 7.5 μg/kg. AUC increased dose-dependently, CL_{tot} (934 to 1090 mL/h/kg), $V_{d,ss}$ (54000 to 67200 mL/kg), and $t_{1/2}$ (38.1 to 49.0 hours) were almost similar across the dose range. No remarkable sex difference was observed in the pharmacokinetic parameters in both rats and dogs.

The major elimination route of E7130 in human is expected to be excretion into feces and urine as an unchanged form with limited contribution of metabolism, and P-gp is mainly involved in the elimination based on the excretion study in rats. In vitro metabolism study with recombinant CYP systems indicated that CYP3A4 is mainly involved in the CYP-dependent metabolism, and other CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A5) were considered to have no or negligible contribution to E7130 metabolism.

Metabolites of E7130 in human, rat, and dog cryopreserved hepatocytes, and recombinant human CYP3A4 were investigated. A total of 16 metabolites were detected at negligible levels in dog and human cryopreserved hepatocytes, recombinant human CYP3A4, or both. No metabolite was detected in rat hepatocytes.

The protein binding of E7130 (0.5 to 50 ng/mL) in plasma was examined by an ultrafiltration method. E7130 showed weak plasma protein binding, and the unbound fraction of E7130 in plasma (fu,plasma) was 0.603 to 0.716 in mouse, 0.547 to 0.631 in rat, 0.506 to 0.558 in dog, and 0.714 to 0.780 in human. No significant species differences or concentration dependency of E7130 were observed in protein binding.

Direct and time-dependent inhibition of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) by E7130 was evaluated in human liver microsomes. E7130 showed direct inhibition of CYP3A when midazolam was used as the probe substrate, and the IC_{50} value was 9.5 μmol/L. E7130 showed no or minimal inhibitory effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (testosterone) up to 10 μmol/L (IC_{50} values >10 μmol/L). No time-dependent inhibition was observed in all CYP isoforms examined.

CYP induction potential of E7130 was evaluated by using cryopreserved human hepatocytes from 3 donors. E7130 did not increase CYP1A2, CYP2B6, and CYP3A4 mRNA levels up to

100 nmol/L; however, E7130 reduced mRNA levels of all 3 tested CYP isoforms at 1 nmol/L or greater, the degree of which was variable depending on the donors.

7.2.3 Toxicology

In a single intravenous dose range finding study in rats (20, 50, and 100 μg/kg), there was no death up to 100 μg/kg, but 100 μg/kg was considered close to lethal dose because of decreased body weight and food consumption. Test article-related changes were dose-dependent hematopoietic suppression, gastrointestinal changes, and increased apoptotic figures in many organs including testes. Except for testicular changes, all the changes showed the tendency of reversibility by 7 days after dosing.

In a single intravenous dose range finding study in dogs (5 and 10 μg/kg), 1 male at 10 μg/kg sacrificed moribund 6 days after dosing. The cause of death was considered bacterial pneumonia secondary to hematopoietic suppression. Test article-related changes were dose-dependent hematopoietic suppression and gastrointestinal changes at 5 μg/kg and above.

In the repeated-dose toxicity study in rats, E7130 was intravenously administrated 2 times every 2 weeks to rats at 20, 50, and 75 μg/kg. Main groups were sacrificed 3 days after second dosing, and recovery animals were sacrificed 14 days after second dosing. One male at 75 μg/kg was found dead 6 days after second dosing, and cause of death was considered as secondary infection. Primary test article-related changes were hematological changes related to hematopoietic suppression and increased apoptotic figures in skin at 20 μg/kg and above, gastrointestinal changes (villous atrophy of digestive tract mucosa, crypt hyperplasia), testicular hypocellularity, and increased apoptotic figures in multiple organs at 50 μg/kg and above, and secondary infections due to hematopoietic suppression at 75 μg/kg. Most changes except for testicular changes showed the tendency of reversibility after 2-week recovery period.

In the repeated-dose toxicity study in dogs, E7130 was intravenously administrated 2 times every 2 weeks to beagle dogs at 2, 5, and 7.5 μg/kg. Main groups were sacrificed 3 days after second dosing, and recovery animals were sacrificed 14 days after second dosing. There was no morbidity or mortality at any dose. Test article-related changes were temporal mucous or soft stool followed by decrease in body weight and food consumption at 7.5 μg/kg, and these changes were resolved after recovery period. Primary test article-related changes were hematological changes related to hematopoietic suppression. Most changes showed the tendency of reversibility after 2-week recovery period because the changes were resolved or accompanied by compensatory/regenerative changes.

7.2.4 Expected Adverse Drug Reactions from Non-clinical toxicity Studies

Hematopoietic suppression, gastrointestinal toxicity, and testicular toxicity are considered the potential risk identified in E7130 studies. Based on the toxicity studies, hematological changes are considered to be appeared from lower dose than other toxicity, and can be monitored by standard laboratory tests in clinical studies.

7.3 Study Rationale

7.3.1 Guidelines and Guidance

This study was designed according to the following guidelines and guidance: "The Guidelines for Clinical Evaluation of Anti-Cancer Drugs in Japan (Notification No. 1101001 dated November 1, 2005), "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH S9; Notification No. 0604-1, dated June 4, 2010), "Guidance for Establishing Safety in First-in-Human Studies during Drug Development" (Notification No. 0402-1, dated April 2, 2012), and the "Technical Guidance on In Vitro Companion Diagnostics and Corresponding Therapeutic Products" (Administrative Notice, dated December 26, 2013).

7.3.2 Rationale for Choice of Starting Dose

The starting dose of E7130 in this study was chosen based on the guidelines in "Nonclinical Evaluation for Anticancer Pharmaceuticals" (ICH S9; Notification No. 0604-1, dated June 4, 2010). According to this guideline, a common approach for many small-molecules is to set a starting dose at 1/10 the Severely Toxic Dose in 10% of the animals (STD_{10}; dose that is associated with lethality, life-threatening toxicities, or irreversible toxicities) in rodents, or at 1/6 the Highest Non-Severely Toxic Dose (HNSTD) in the case where non-rodents are the most appropriate test species. In the repeated-dose toxicity study in rats, 1 animal out of 12 was found dead at 75 μg/kg. Therefore, 75 μg/kg (450 $\mu g/m^2$) was considered to be approximately STD_{10}. In the repeated-dose toxicity study in dogs, although there were toxic findings at the high dose 7.5 μg/kg, they were not severe and reversibility of the findings were confirmed. Therefore, 7.5 μg/kg (150 $\mu g/m^2$) was considered to be HNSTD. Furthermore, based on the results of nonclinical studies (pharmacokinetics, primary Pharmacodynamics), the lower limit of dosage which can be expected to be effective in humans was estimated to be 37 to 85 $\mu g/m^2$. From the above results, dogs were considered to be appropriate species for choice of starting dose, and 1/6 of HNSTD (25 $\mu g/m^2$) was selected as starting dose for the first clinical study with E7130.

7.3.3 Rationale for every-2-week/every-3-week Dosing

In preclinical FaDu xenograft models, antitumor effects of E7130 were compared in 2 schedules of E7130 administration : Once 7 days (Q7D) ×2 at 100 μg/kg, and Once 2 days (Q2D) ×3 for 2 weeks at 33 μg/kg in both monotherapy and combination therapy with cetuximab. In this comparison, even though the total amount of administered E7130 is identical, their antitumor efficacies are quite different, and the former schedule showed more potent tumor growth delay (monotherapy) and tumor shrinkage (combination therapy) than the later one. The result suggested that the high-dose administration showed a superior efficacy to the low-dose intermittent administrations when the same amount of the drug was injected. In addition, in the repeated toxicity study in dogs, after 2-week recovery period, the hematopoietic suppression-related changes showed the tendency of reversibility. And a 2-week interval was considered sufficient to recover from hematopoietic suppression. Then, we decided to administer E7130 in every-2-week or every-3-week schedule considering combination regimen with other agents in future clinical development.

7.3.4 Rationale for Modified Toxicity Probability Interval (mTPI) Design Applying Single-Patient DLT-evaluation for Low-toxic Dose in Part 1

In Part 1, the MTD will be determined by allocating subjects to doses according to a Modified Toxicity Probability Interval (mTPI) design. The mTPI design is a Bayesian adaptive allocation method that is different to the commonly used 3+3 design that enables the true MTD (one that corresponds to the target DLT rate) to be more precisely selected based on a statistical framework (Ji Y and Wang SJ, 2013). Similarly, numerous reports in the literature have reported that the Continual Reassessment Method (CRM), a well-known Bayesian adaptive allocation method, and the extended CRM have superior operating characteristics as well as being able to select the MTD more accurately than the 3+3 design (Thall PF and Lee SJ, 2003; Iasonos A, et al., 2008; Le Tourneau C, et al., 2009). However, since this design is based on complicated dose-response models, it is necessary to carefully configure the initial settings prior to starting the study in order to obtain the desired operating characteristics or implement an organizational structure that allows the treating physician to know, in a timely manner, the dose to allocate to the next subject (Ji Y, et al., 2010). Factors such as the availability of free software have made it easier to implement these study designs in recent years, and while the number of studies employing these designs is increasing, the reality is that such designs, despite their superior operating characteristics, are still not popular as many still favor the simpler 3+3 design (Ji Y and Wang SJ, 2013).

In contrast, the mTPI design can be easily applied in a similar manner to the 3+3 design as it does not require the use of complicated dose-response models, and reports in the literature have shown through simulations that its operating characteristics are non-inferior to the CRM (Ji Y, et al., 2010). In addition, compared to the CRM, the mTPI design is safer for subjects since it can, on average, minimize the proportion of subjects that develop DLT during a study or allocate fewer subjects to toxic doses that exceed target DLT rates (Ji Y, et al., 2010). The mTPI design was also presented at the 2013 ASCO Pre-Annual Meeting Seminar, and numerous studies implementing the design have also been reported in recent years (Ji Y and Wang SJ, 2013).

The original mTPI design has 1 cohort size (eg, 2 or 3 subjects) during the study. But this study allows to escalate dose with single-patient DLT evaluation until Grade 2 or higher drug related toxicity is observed in the every-2-week regimen although the initial cohort size in the every-2-week regimen is 3 subjects. If such a toxicity is observed, the single patient cohort will be expanded to larger cohort size to evaluate safety and find MTD carefully. This modification to original mTPI design will reduce patients treated at sub-therapeutic doses and enhance the probability of investigating doses around MTD. The dose finding for the every-3-week regimen will start using the original mTPI design because the starting dose will be equal to or around the MTD of the every-2-week regimen and already close to one of the every-3-week regimens.

As a result, the mTPI design with the modification will be adopted for the allocation of doses to subjects in Part 1.

7.3.5 Rationale for the Method of Deciding the Dose of the Next Dose Group

In the Phase 1 study of an anticancer agent, it is considered important to minimize the number of subjects receiving treatment in low dose groups where it is difficult to expect biological activity from the drug, and to escalate doses with careful consideration for safety in high dose groups where the development of toxicity is anticipated (Simon R, et al., 1997). In light of these conditions, in this study subjects in the low dose group will receive a 100% dose escalation only if they developed a Grade 1 or lower toxicity, whereas for the higher dose groups a dose escalation method that limits the escalation to 50% or 33% of the prior dose, depending on the severity of the toxicity seen, was adopted with giving sufficient consideration to the occurrence of toxicity. As dose escalations are tailored according to the severity of toxicities seen in each dose group, this is an ethical method for dose escalations where the safety of subjects can be ensured.

7.3.6 Rationale for Target Cancer Types in Part 2

The target indications were selected among the cancer which can be expected the effect of tumor microenvironment (TME) on E7130. The main TME effects of E7130 are vascular remodeling effect and suppression of the activated population of CAFs. There are multiple number of reports which indicate that hypoxic condition in those tumors including BC, SCCHN and UC gives worse impact on the patient survival (Wilson WR and Hay MP, 2011; Semenza GL, 2007; Yang L, 2017). Regarding CAFs, high expression of CAFs marker in those cancers including non-small cell lung cancer, BC, esophagus cancer, colorectal cancer (CRC), pancreatic cancer, small cell lung cancer, SCCHN and UC are reported to closely relate with poor treatment and outcome (De Vlieghere E, et al., 2015; Knops AM, 2020; Goulet CR, 2019). E7130 is expected to inhibit infiltration and metastasis of cancer cells based on its TME effect in addition to its direct antitumor effect by inhibiting microtubule polymerization.

[Added in the protocol version 6]

7.3.6.1 Squamous cell carcinoma of the head and neck (SCCHN)

In the dose-escalation portion of this study, the antitumor effect of E7130 against esophageal squamous cell carcinoma was demonstrated, and a nonclinical exploratory study showed the tumor growth inhibitory effect of E7130 against SCCHN. Therefore, E7130 is expected to have an antitumor effect against squamous cell carcinoma. It was decided to further investigate the safety and efficacy of E7130 in subjects with unresectable SCCHN and to explore PD markers using tumor tissues and imaging biomarkers. The standard first-line therapy for unresectable SCCHN is immune checkpoint inhibitors or platinum-based combination chemotherapy. Cytotoxic drugs including taxanes and immune checkpoint inhibitors have been approved as second-line therapies, but there is no standard therapy. Consequently, in order to conduct the study in a population of patients with unresectable SCCHN and a certain history of treatment who previously received at least 1 regimen of systemic therapy, the number of prior systemic therapy regimens for advanced/metastatic cancer allowed was specified to be up to 3.

7.3.6.2 Urothelial carcinoma

Since the antitumor effect of E7130 was demonstrated for UC in the dose-escalation portion of this study, it was decided to further investigate the safety, efficacy, etc., of E7130 for unresectable UC. The first-line treatment of unresectable UC consists of platinum-based combination chemotherapy followed by maintenance therapy with avelumab alone. Cytotoxic drugs including taxanes and immune checkpoint inhibitors have been approved as second-line therapies, but there is no standard therapy. Consequently, in order to conduct the study in a population of patients with unresectable UC and a certain history of treatment who previously received platinum agents and immune checkpoint inhibitors, the number of prior systemic therapy regimens for advanced/metastatic cancer allowed was specified to be up to 3.

[Added in the protocol version 8]

7.3.6.3 Regimens and doses to be used in Part2

In the protocol version 6 , based on the results of the safety, efficacy, and biomarkers in Part 1, the regimen and dose to be used in Part 2 were selected to be 480 μg/m^2, which is the MTD of the every-3-week regimen. Thereafter, treatment postponement/dose reductions/study discontinuations due to events such as Grade 3 peripheral sensory neuropathy and Grade 3 ileus occurred in several of the first 8 subjects in Part 2 who started using these regimen and dose. Therefore, it was found to be appropriate to reduce the regimen and dose to be used in Part 2 to 410 μg/m^2 every 3 weeks in the protocol version 8.

[Added in the protocol version 10]

7.3.6.4 Regimens and doses to be used in Part2

In the protocol version 8, the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks based on the safety results in the first 8 subjects in the 480 μg/m^2 every 3 weeks group in Part 2. However, it was subsequently judged appropriate to reduce the regimen and dose to be used in Part 2 to 350 μg/m^2 every 3 weeks based on the overall safety up to C3D1 in the first 10 subjects starting from Part 2 using the regimen and dose as described in the protocol.

8 STUDY OBJECTIVES

8.1 Primary Objective(s)

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

8.2 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) of E7130 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).

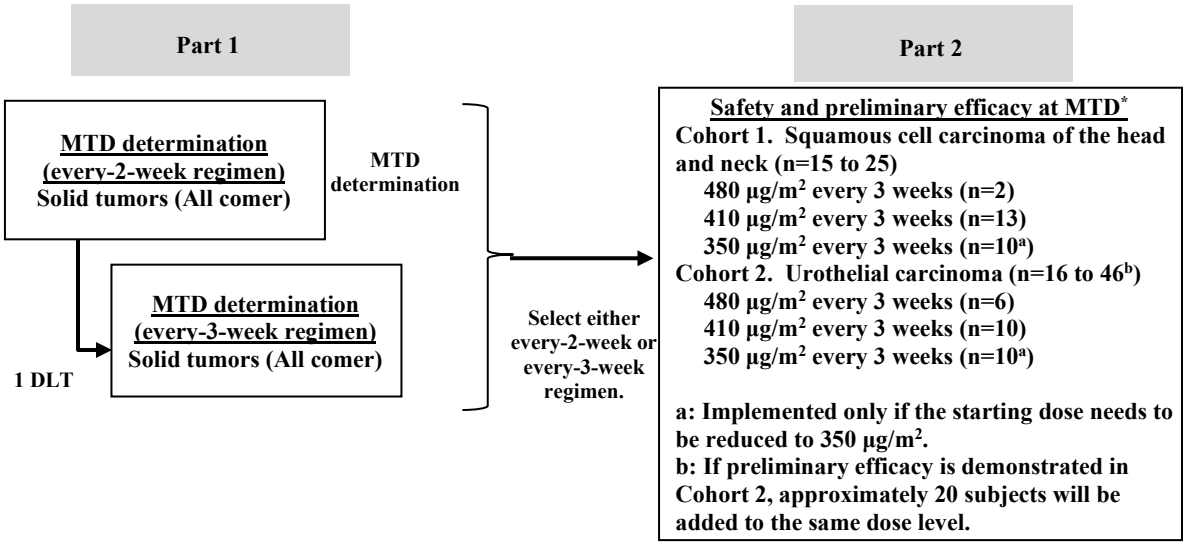
8.3 Exploratory objectives



9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 1 study of E7130 in subjects with solid tumors. This study will be conducted in 2 parts (Part 1 and Part 2). Part 1 will assess dose-limiting toxicity (DLT) when E7130 is administered to subjects with solid tumors and determine the MTD. Efficacy, safety, PK, and biomarkers will be evaluated to select the regimen and dose to be used in Part 2 from either of the every-2-week and every-3-week regimens that were evaluated in Part 1 (The regimen and dose to be used in Part 2 had been determined to be the MTD of 480 μg/m^2 every 3 weeks [added in the protocol version 6]) (Based on the safety results of 480 μg/m^2 [every-3-week regimen] in the first 8 subjects in Part 2, the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks). In addition, the regimen and dose used in Part 2 may be reduced to 350 μg/m^2 every 3 weeks based on the safety of the first 10 subjects (total of Cohorts 1 and 2) receiving 410 μg/m^2 every 3 weeks. If Grade 3 or higher peripheral sensory neuropathy and/or Grade 3 or higher ileus attributable to neuropathy occurred in ≥3 of the first 10 subjects by C3D1, the dose should be reduced to 350 μg/m^2. Furthermore, a dose reduction to 350 μg/m^2 may be decided in consultation between the sponsor and the investigator based on the overall safety up to C3D1. In order to ensure the safety of each subject, the conditions of subjects will be checked more frequently than the specified schedule as necessary, and AEs will be evaluated as needed. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2, approximately 20 subjects will be added to that dose level. CR and PR require confirmation by the subsequent response assessment at 4 weeks or later [added in the protocol version 8]). Part 2 will consist of 2 cohorts to further characterize the tolerability and safety of E7130 and to evaluate the preliminary efficacy of E7130 at the MTD in subjects with squamous cell carcinoma of the head and neck (SCCHN) in Cohort 1 and urothelial carcinoma (UC) in Cohort 2. The RD of E7130 for future studies will be estimated based on the data from Part 1 and Part 2.



* The regimen and dose to be used in Part 2 had been determined to be the MTD of 480 µg/m^2 every 3 weeks [added in the protocol version 6]. Based on the safety results of 480 µg/m^2 (every-3-week regimen) in the first 8 subjects in Part 2, the regimen and dose to be used in Part 2 were changed to 410 µg/m^2 every 3 weeks. In addition, the regimen and dose used in Part 2 may be reduced to 350 µg/m^2 every 3 weeks based on the safety of the first 10 subjects (total of Cohorts 1 and 2) receiving 410 µg/m^2 every 3 weeks. If Grade 3 or higher peripheral sensory neuropathy and/or Grade 3 or higher ileus attributable to neuropathy occurred in ≥3 of the first 10 subjects by C3D1, the dose should be reduced to 350 µg/m^2. Furthermore, a dose reduction to 350 µg/m^2 may be decided in consultation between the sponsor and the investigator based on the overall safety up to C3D1. In order to ensure the safety of each subject, the conditions of subjects will be checked more frequently than the specified schedule as necessary, and AEs will be evaluated as needed. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2, approximately 20 subjects will be added to that dose level. CR and PR require confirmation by the subsequent response assessment at 4 weeks or later [added in the protocol version 8].

Figure 9-1 Study Design Overview

MTD = maximum tolerated dose

9.1.1 Part 1

The study design of Part 1 is presented in Figure 9-2.

Part 1 will be conducted in subjects with solid tumors. Part 1 will consist of a Pretreatment Phase, Treatment Phase, and Follow-up Phase.

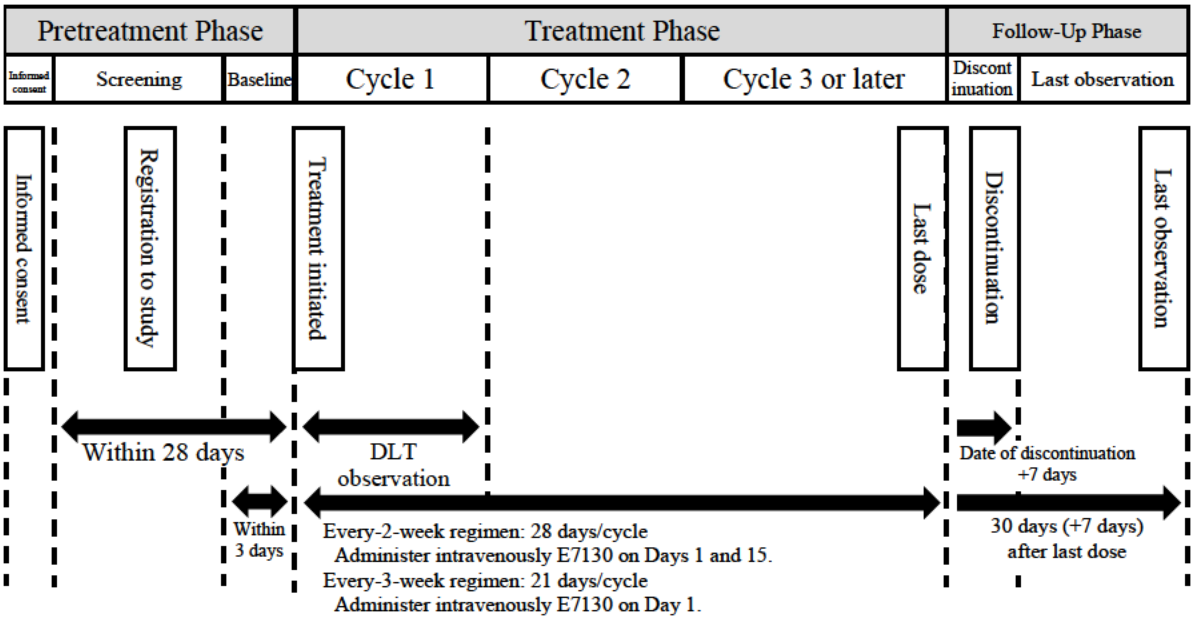


Figure 9-2. Study Design of Part 1

DLT = dose limiting toxicity.

First, DLT with the every-2-week regimen will be assessed, and then DLT with the every-3-week regimen will be assessed.

9.1.1.1 Pretreatment Phase

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

Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. After obtaining the informed consent, screening will last no longer than 28 days before the treatment. After screening assessments, subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled. Baseline assessments will be conducted within 3 days before the treatment in order to confirm the eligibility and disease condition of the subjects before moving to the Treatment Phase.

9.1.1.2 Treatment Phase

The Treatment Phase will consist of Cycle 1 for DLT assessment with the every-2-week and every-3-week regimens and subsequent cycles for sequence treatment. First, DLT assessment will be initiated to determine the MTD of the every-2-week regimen. After the first DLT with the every-2-week regimen is identified, DLT assessment will be initiated to determine the MTD of the every-3-week regimen. The starting dose of the every-3-week regimen will be one level lower dose of the dose at which the first DLT occurred with the every-2-week regimen. The DLT assessment with the every-2-week and every-3-week

regimens will be performed in parallel. Based on the results of DLT assessment including a PK profile of the every-2-week regimen, DLT assessment with the every-3-week regimen may be started before the first DLT with the every-2-week regimen is observed. For Cycle 1 and onward, each cycle is 28 days long for the every-2-week regimen and 21 days long for the every-3-week regimen. In Cycle 1 and onwards, subjects will be administered E7130 every 2 weeks (Days 1 and 15 of each cycle) or every 3 weeks (Day 1 of each cycle) until they meet any of the criteria in the "Criteria for discontinuation" (see Section 9.3.3.1).

Considering visit schedule and safety, in the dose escalation cohort, subjects will be admitted to the hospital from the day before Cycle 1 Day 1 (C1D1) to Cycle 2 Day 2 (C2D2) (for safety assurance, up to the end of Cycle 1 [DLT evaluation period]) as a rule. For the continuation of Cycle 2 or later administration, informed consent should be obtained before initiating the study or before entering Cycle 2.

Subjects who will discontinue the study treatment will move to the Follow-up Phase.

9.1.1.3 Follow-Up Phase

The Follow-up Phase will consist of the examination at study discontinuation and the last observation visit.

The examination at study discontinuation will be performed within 7 days after treatment discontinuation is determined by the investigator or subinvestigator.

The last observation visit will occur 30 days (+7 days) after the last dose of the study drug. If a new anticancer agent needs to be immediately started due to deterioration in the subject's condition, the last observation visit can be conducted before 30 days after the last dose of the study drug has passed.

9.1.1.4 Dose escalation and 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, the MTD of E7130 for the every-2-week regimen will be determined in the following manner. The initial dose level of E7130 for the every-2-week regimen will be 25 $\mu g/m^2$, and the first cohort would enroll 3 subjects for DLT evaluation. In the first cohort only, initial administration of E7130 in the second subject must be started on or after the 29th day after C1D1 of the first subject. If drug-related Grade 2 or higher toxicity excluding clinically insignificant events occurred 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 excluding clinically insignificant events is NOT identified in the initial cohort, DLT will be evaluated at successive dose levels in a single subject each until such a toxicity occurs. If such a toxicity is observed, the cohort will be expanded to enroll a total of 3 subjects.

After that, each subject will be assigned to a dose of E7130 in accordance with the rules of the mTPI design based on a target DLT rate of 25% in this study 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 the "Decision Rule for Dose Assignment (Table 1)" below (see Appendix 1 for the detail).

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,
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 may be considered.

The DLT assessment and the next dose level will be selected based on the results of the 3-subject cohort using the mTPI design. Based on the number of subjects developing DLT(s) during the DLT assessment period at each dose level, dose assignment (escalate, stay, de-escalate) for the next 3 subjects will be determined according to the above Table 1. However, the dose assignment for the next 3 subjects can be determined by taking into consideration the treatment compliance in Cycle 2, etc., in addition to the number of subjects who developed DLTs. When 1 subject has already been evaluated at the next dose level, 2 subjects will be enrolled, and dose assignment will be determined based on the results from the 3 subjects. In the case where 4 or more subjects were enrolled and evaluated in a cohort, dose assignment will be decided based on the results from all the subjects at the dose. The next cohort at the dose level will enroll and assess 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 assessed as the another cohort. At the new dose level where 3 subjects (except for the initial dosing cohort of the every-2-week regimen) are enrolled, the second subject

should start to receive the initial administration of E7130 on or after the following day after the first subject is observed on C1D1. Subjects who are not evaluable for DLT (for example, those 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 each (except for initial dosing cohort), the MTD for the every-2-week regimen will be determined. However, the maximum number of cohorts may be adjusted as required. In addition, early determination of MTD may be considered if the probability of future subjects also being allocated to that dose is expected to be high enough. The details of this design are described in the Section "9.7 Statistical Methods."

The dose escalation range is 100% until development of drug-related Grade 2 toxicity in 1 subject. The range would be switched to 50% after development of such a toxicity. When drug-related Grade 2 in ≥2 subjects during study and/or Grade 3 or higher toxicity in ≥1 subject occurred, the dose escalation range would be switched to 33%. The dose escalation ranges are summarized in the table below. If a 100% or 50% dose escalation resulted in "De-escalate" in the above table, then an intermediate dose level between pre-dose escalation and post-one would be evaluated in the next cohort. When escalating to the next dose level according to the mTPI design, and if there is a higher dose level that has been tested previously, the higher dose recently studied will be assessed in the next cohort without applying the "Method for deciding the dose of the next cohort (Table 2)." However, doses other than the abovementioned ones may be evaluated after consultation among the investigator, sponsor, and medical expert.

Table 2 Method for deciding the dose of the next cohort

Dose escalation for the next cohort (%)	Drug-related toxicity that developed during Cycle 1
100	Grade ≤1 only
50	Grade 2 in 1 subject
33	Grade 2 in ≥2 subjects during study and/or Grade ≥3 in ≥1 subject

(*) Excluding clinically insignificant events (eg, alopecia or abnormal laboratory parameters not requiring medical treatment) as this toxicity for deciding the dose of the next cohort.

If a fraction is included in the theoretical value calculated by the determination method above for the dose of the next cohort, the value will be rounded off according to the following rules to derive the actual dose.

- If the theoretical value is ≥25 μg/m^2 and <100 μg/m^2: The value will be rounded off to the nearest integer to derive the actual dose.
- If the theoretical value is ≥100 μg/m^2 and <1000 μg/m^2: The value will be rounded off to the 2nd integer (ten's place) to derive the actual dose.

- If the theoretical value is ≥1000 μg/m^2: The value will be rounded down to the 1st integer (one's place) and rounded off to the 2nd integer (ten's place) and derive the actual dose (eg, in the case of 1346 μg/m^2, actual dose is 1300 μg/m^2).

Transition to the next cohort and dose assignment, dose escalation range, transition timing of DLT assessment for the every-3-week regimen, initial dose of the every-3-week regimen, and transition timing to Part 2 will be decided based on the discussions among the investigator, sponsor, and medical expert. If necessary, the suggestions from independent medical advisors will be sought for this purpose.

A dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate for each dose will be defined as the MTD of the every-2-week regimen. Once the MTD is selected in accordance with this procedure, the MTD will be finally determined while taking toxicity data up to Cycle 2 into account. After the first DLT with the every-2-week regimen is identified, DLT assessment will be initiated to determine the MTD of the every-3-week regimen. The starting dose of the every-3-week regimen will be one level lower dose of the dose at which the first DLT occurred with the every-2-week regimen. Based on the results of DLT assessment including the PK profile of the every-2-week regimen, DLT assessment of the every-3-week regimen may be started before the first DLT with the every-2-week regimen is observed. The initial dose level of E7130 for the every-3-week regimen will be decided based on the safety profile of the every-2-week regimen, and the first cohort would enroll 3 subjects for DLT evaluation.

The dose assignment rules for the every-3-week regimen are also determined by mTPI method described above. To determine dose assignment for the every-3-week regimen, the DLT evaluation results at the same dose level in the every-2-week regimen will not be pooled. When DLT evaluation is completed in 5 cohorts being composed of 3 subjects, the MTD for the every-3-week regimen will be selected in the same manner as that for the every-2-week regimen. However, the maximum number of cohorts may be adjusted as required. The dose escalation range for every-3-week dose finding will be decided according to the "Method for deciding the dose of the next cohort(Table 2)," and the maximum range is 50%.

If there are subjects who could not complete infusion of E7130 on C1D1 and C1D15 (every-2-week regimen only) or the DLT assessment of a 28-day (every-2week regimen) or 21-day (every-3-week regimen) period following the first dose of E7130 because of any reasons except DLTs, the sponsor should discuss whether the subjects should be included in the DLT Analysis Set with the investigator, medical expert and if necessary, independent medical advisors. Based on the discussion, the sponsor can also replace DLT evaluable subjects by enrolling additional subjects.

In addition, transition to the next dose levels and dose escalation range will be decided while taking into account of the safety data of those subjects who were excluded from the DLT Analysis Set as well.

Example of Dose Escalation and Dose Assignment of Subjects

Figure 9-3 shows an example of dose escalation and dose assignment of subject by an accelerated mTPI design from initial cohort through close of subject registration in every-2-week regimen.

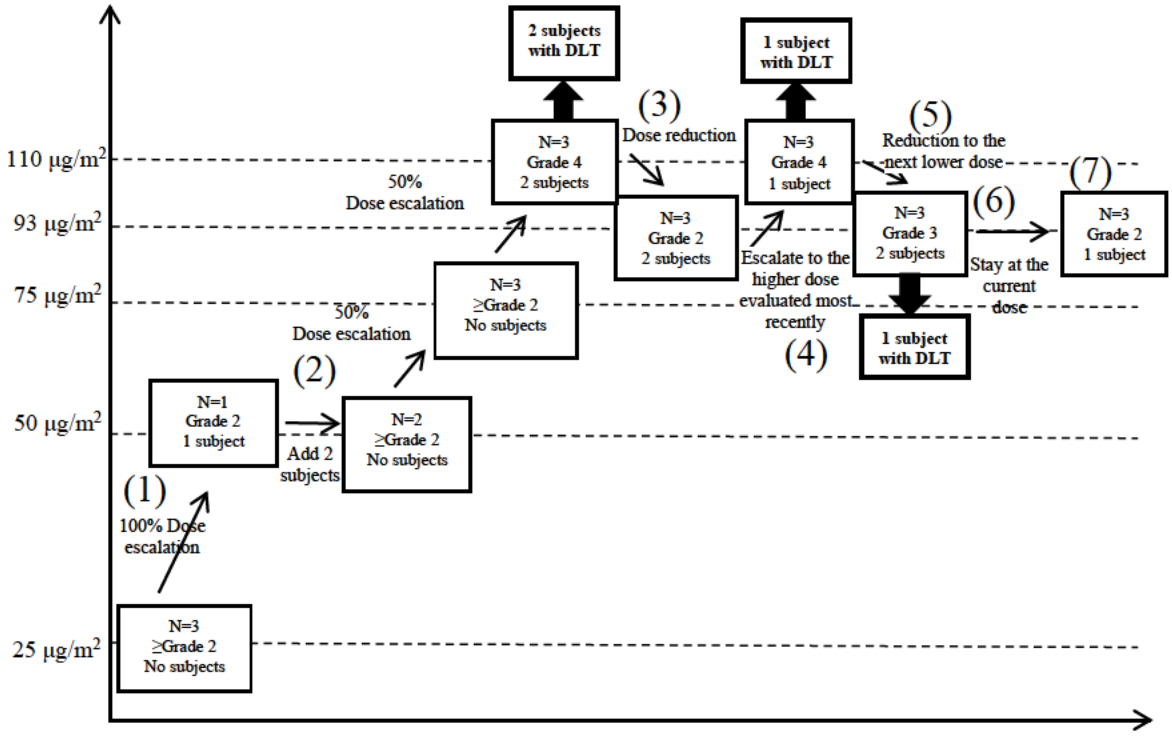


Figure 9-3 Example of Dose Escalation and Dose Assignment of Subjects (every 2 weeks)

The grades and the number of subjects in the figure represent the number of subjects who develop study drug-related toxicities at the relevant grade in Cycle 1.

(1) In 3 subjects treated at 25 µg/m^2 (first dose cohort of the every-2-week regimen), Grade 2 or higher study drug-related toxicity (hereinafter, "adverse drug reaction") was not observed in Cycle 1. Therefore, the dose for the next cohort will be 50 µg/m^2 (100% dose escalation) according to the "Method for Deciding the Dose of the Next Cohort (Table 2)." Thereafter, the dose will be escalated (100% dose escalation) in a single subject each until a Grade 2 or higher adverse drug reaction occurs.

(2) One subject treated at the 50 µg/m^2 newly developed a Grade 2 adverse drug reaction that was not defined as DLT. Therefore, this 50 µg/m^2 cohort was expanded to evaluate DLT in 3 subjects by adding 2 subjects. From this point of time, dose assignment to subjects was supposed to be determined according to the "Decision Rule for Dose Assignment (Table 1)."

Two subjects added to the 50 μg/m^2 cohort did not develop DLT or Grade 2 or higher adverse drug reactions. Since evaluation in 1 subject of the 25 μg/m^2 cohort and a total of 3 subjects in the 50 μg/m^2 cohort demonstrated that no DLT developed in 0 subjects and Grade 2 adverse drug reactions developed in 1 subject, the dose for the next cohort will be 75 μg/m^2 according to the rules "E: Escalate to the next higher dose (See Table 1)" and "50% dose escalation (See Table 2)".

(3) DLT was observed in 2 out of 3 subjects in the 110 μg/m^2 cohort, therefore, the rule "D: De-escalate to the next lower dose" will be applied to the dose for the next cohort. However, the calculated dose (110 μg/m^2) is a 50% dose escalation from the dose for the previous cohort (75 μg/m^2) for which the rule "Escalate to the next higher dose" is not applicable, therefore, the dose for the next cohort will be an intermediate dose between 110 μg/m^2 and 75 μg/m^2, ie, 93 μg/m^2.

(4) Grade 2 adverse drug reactions were observed in 2 out of 3 subjects in the 93 μg/m^2 cohort, but no DLTs were observed, therefore, the rule "E: Escalate to the next higher dose" will be applied to the dose for the next cohort according to Table 1. However, as a dose higher than 93 μg/m^2 has already been evaluated, the dose for the next cohort will be higher than 93 μg/m^2 (ie, 110 μg/m^2 which has been most recently evaluated), instead of applying Table 2.

(5) DLT was observed in 1 out of 3 subjects in this 110 μg/m^2 cohort, and a total of 3 out of 6 subjects treated at 110 μg/m^2 developed DLT; therefore, the dose for the next cohort will be 93 μg/m^2 by applying the rule "D: De-escalate to the next lower dose" according to Table 1.

(6) DLT was observed in 1 out of 3 subjects in this 93 μg/m^2 cohort, and a total of 1 out of 6 subjects treated at 93 μg/m^2 developed DLT, therefore, the dose for the next cohort will remain at 93 μg/m^2 by applying the rule "S: Stay at the current dose" according to Table 1.

(7) As DLT evaluations in a total of 7 cohorts (except for the first dose cohort) have been completed, subject registration in the every-2-week regimen will be closed to determine the MTD.

9.1.1.5 Determination of MTD regimen to be used in Part 2

The dosing regimen to be used in Part 2 will be selected after the MTDs of the every-2-week and every-3-week regimens are determined. However, based on preclinical and clinical findings (including safety and tolerability, PK, efficacy, and biomarker findings from Part 1), the dosing regimen can also be defined after determination of the MTD of either every-2-week or every-3-week regimen.

[Added in the protocol version 6]

The dose regimen to be used in Part 2 was chosen to be the every-3-week regimen (MTD 480 μg/m^2).

[Added in the protocol version 8]

Based on the safety results of 480 μg/m^2 (every-3-week regimen) in the first 8 subjects in Part 2, the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks. In addition, the regimen and dose used in Part 2 may be reduced to 350 μg/m^2 every 3 weeks based on the safety of the first 10 subjects (total of Cohorts 1 and 2) receiving 410 μg/m^2 every 3 weeks. If Grade 3 or higher peripheral sensory neuropathy and/or Grade 3 or higher ileus attributable to neuropathy occurred in ≥3 of the first 10 subjects by Cycle 3 Day 1 (C3D1), the dose should be reduced to 350 μg/m^2. Furthermore, a dose reduction to 350 μg/m^2 may be decided in consultation between the sponsor and the investigator based on the overall safety up to C3D1. In order to ensure the safety of each subject, the conditions of subjects will be checked more frequently than the specified schedule as necessary, and AEs will be evaluated as needed. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2, approximately 20 subjects will be added to that dose level. CR and PR require confirmation by the subsequent response assessment at 4 weeks or later.

9.1.2 Part 2

Part 2 will consist of 2 cohorts, and the MTD for the dosing regimen determined in Part 1 will be used. The study design of Part 2 is presented in Figure 9-4. Enrollment of subjects in each cohort will occur in parallel. Cohort 1 (SCCHN) will consist of approximately 15 to 25 subjects, and Cohort 2 (UC) will consist of approximately 16 to 46 subjects. Part 2 will consist of a Pretreatment Phase, Treatment Phase, and Follow-Up Phase.

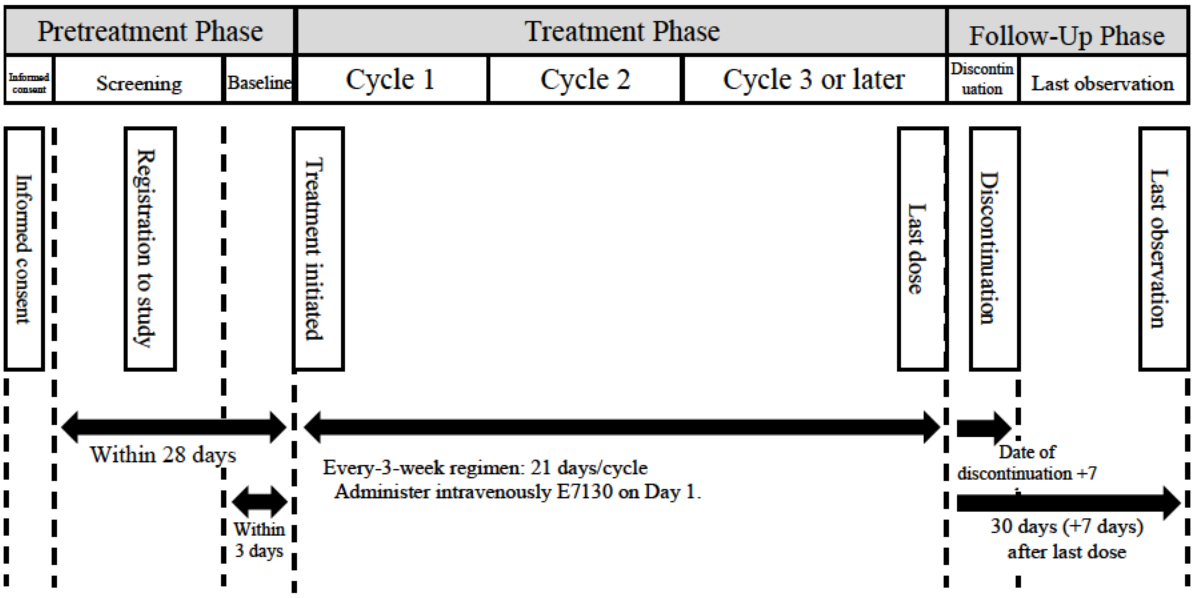


Figure 9-4 Study Design of Part 2

9.1.2.1 Pretreatment Phase

The Pretreatment Phase will involve obtaining informed consent, a screening period, and a baseline assessment. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. After obtaining the informed consent, screening will last no longer than 28 days before the treatment. After screening assessments, subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled. Baseline assessments will be conducted within 3 days before the treatment in order to confirm the eligibility and disease condition of the subjects before moving to the Treatment Phase.

9.1.2.2 Treatment Phase

The Treatment Phase will consist of treatment cycles that are each 21 days (every-3-week regimen) in duration , and administration of E7130 every 3 weeks will continue until subjects meet any of the criteria in the "Criteria for discontinuation" (see Section 9.3.3.1). Subjects who will discontinue the study treatment will move to the Follow-up Phase.

9.1.2.3 Follow-Up Phase

The Follow-up Phase will consist of the examination at study discontinuation, the last observation and the follow-up for OS. The examination at study discontinuation will be performed within 7 days after treatment discontinuation is determined by the investigator or subinvestigator. The last observation visit will occur 30 days (+7 days) after the last dose of the study drug. If a new anticancer agent needs to be immediately started due to deterioration in the subject's condition, the last observation visit can be conducted before 30 days after the last dose of the study drug has passed. In the follow-up for OS, the subjects' survival and post-anti-cancer treatment after discontinuation of treatment with E7130 will be followed every 6 months (approximate) and if requested by the sponsor up to 18 months after enrollment of the last subject.

9.1.3 RD Determination

The RD will be selected based on the MTD, efficacy, safety, PK profile and biomarker data in Part 1 and Part 2.

9.2 Discussion of Study Design, Including Choice of Control Groups

The rationale of the study design is described in "7.3 Study Rationale."

9.3 Selection of Study Population

In Part 1, approximately 40 subjects will be enrolled at 1to 2 sites in Japan. In Part 2, approximately 30 to 50 subjects will be enrolled at multiple sites (9 to 11 sites planned) in Japan. If the starting dose is reduced to 350 μg/m^2, approximately 20 additional subjects may be enrolled. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Subjects who have provided voluntary written consent for participation in this clinical study.
2. Subjects to whom the rules for complying with this clinical study have been adequately explained, and who intend to and can comply with these rules.
3. Subjects aged ≥20 years at the time of informed consent.
4. Part 1: Subjects with a histological and/or cytological diagnosis of solid tumor who failed standard therapies, or for which no appropriate treatment is available.
   Part 2, Cohort 1: Subjects with a histologically documented diagnosis of unresectable SCCHN who previously received at least 1 but no more than 3 regimens of prior systemic therapy for advanced or metastatic disease.
   Part 2, Cohort 2: Subjects with a histologically or cytologically documented diagnosis of unresectable UC of the bladder, urethra, ureter, or renal pelvis who previously received systemic therapy with a platinum and immune checkpoint inhibitor. Systemic therapies for advanced or metastatic disease should be no more than 3 regimens.
5. Subjects with adequate function of major organs.
   a. Hemoglobin ≥9.0 g/dL.
   b. Neutrophil count $\geq 1.5\times10^3/\mu L$.
   c. Platelet count $\geq 10\times10^4/\mu L$.
   d. Total bilirubin ≤1.5× upper limit of normal (ULN) in the facility.
   e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0×ULN in the facility.
      ≤5.0×ULN in the facility for subjects with liver metastases.
   f. Serum creatinine ≤1.5×ULN in the facility or creatinine clearance ≥30 mL/min for subjects with creatinine levels >1.5×ULN in the facility.
6. Subjects with Performance Status (PS) score of 0 to 1 established by Eastern Cooperative Oncology Group (ECOG).
7. Subjects who are expected to survive for 3 months or longer after starting administration of the investigational drug.
8. Washout period required from the end of prior treatment to the first administration of study drug will be as follows.
   a. Anticancer therapy
      - Antibody and other study drugs: >4 weeks. (However, in the case where the half-life of other study drugs is known and 5× half-lives of that study drug is less than or equal to 4 weeks, subjects can be eligible after ≥5× half-lives of that study drug has passed.)
      - Prior chemotherapy (except small-molecule targeted therapy), surgical therapy, radiation therapy: >3weeks.

- Endocrine therapy, immunotherapy (except antibody drug), small-molecule targeted therapy: >2 weeks.

b. Supportive therapies

- Blood/platelet transfusion, hematopoietic stimulating agent including granulocyte colony-stimulating factor (G-CSF) formulation: >2 weeks.

9. Subjects who agree to submit blood samples prior and during study treatment for PD markers.

Inclusion Criteria (Part 2 only)

10. Measurable disease meeting the following criteria:
    a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is serially measurable according to RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI).
    b. Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progressive disease to be deemed a target lesion.
11. (Cohort 1 only) Subjects with a lesion appropriate for biopsies before and after study infusion to be conducted as the biomarker assessment and who agreed to undergo biopsies at pre- and post-treatment, provide tumor tissues, and be included in PGx assessments.
12. (Cohort 1 only) Subjects with a primary lesion, local recurrent lesion, or cervical lymph node (≥2.0 cm) not affected by MRI susceptibility artifacts (eg, excluding bony or maxillary sinus involvement of the palate) that are suitable for imaging biomarker measurement. Lesions used for imaging biomarkers should be different from those for biopsies at pre- and post-treatment unless there is only one appropriate lesion.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Medical history of clinically significant cardiovascular impairment:
    a. Heart disease greater than or equal to New York Heart Association (NYHA) Class II.
    b. Unstable angina pectoris, myocardial infarction or stroke within 6 months before the first dose of study drug.
    c. Prolongation of corrected QT (QTc) interval to >480 msec (Fridericia method).
    d. Arrhythmia associated with hemodynamic instability within 6 months.
2. Serious concomitant systemic infection requiring medical treatment (including bacterial infection and fungal infection).
3. Subjects who test positive for human immunodeficiency virus (HIV antibody).
4. Active viral hepatitis (B or C)(*) as demonstrated by positive serology or requiring treatment.

    (*) HBsAg, anti-HBs/HBcAb and anti-HCV Ab test. Subject who are anti-HBs/HBcAb (+) with less than 20 IU/mL HBV-DNA are eligible.

If HCV antibody is positive, HCV-RNA level will be measured. If negative, the subject can be enrolled.

5. Effusion requiring drainage. (Note: Subject whose symptom has been treated and stable for 2 weeks prior to the first administration of the study drug, is eligible.)
6. Subjects whose toxicity of previous treatment has not recovered to Grade 1 or lower (except for alopecia, and hemoglobin provided in Inclusion Criterion 5).
7. Other active malignancy (except for definitively treated non-invasive melanoma, basal or squamous cell carcinoma of the skin, carcinoma in-situ of the cervix, or carcinoma in situ of bladder) within the past 24 months prior to the first administration of the study drug. Other exclusions (eg, esophageal cancer completely removed by endoscopic treatment) may be considered after discussion and agreement with the sponsor.
8. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] or human chorionic gonadotropin [hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 3 days before the first dose of study drug (breastfeeding subjects are not eligible even if they discontinue breastfeeding).
9. Women of childbearing potential or man of impregnate potential who do not agree that both the subject and his/her partner will use a medically effective method for contraception (as below Note 2)) during the study and after study drug discontinuation (male; 90 days, female; 60 days)Note 1).

   Note 1) The reporting period may be extended based on the half-life of E7130 calculated from this trial.

   Note 2) Condom,* contraceptive sponge,** foam,** jelly,** diaphragm,* intrauterine device (IUD),* or use of oral contraception* from at least 4 weeks before starting the study treatment
   (*Approved drugs or certified medical devices in Japan, **Non-approved drugs or certified medical devices in Japan).
10. Known intolerance to the study drug or any of the excipients.
11. Any medical or other condition that in the opinion of the investigator(s) would preclude the subject's participation in the study.
12. Scheduled for surgery during the study.
13. Diagnosed with meningeal carcinomatosis.
14. Subjects with brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.

Exclusion Criteria (Part 2 only)

15. (Cohort 1 only) Subjects with a past or current history of medical conditions interfering with the imaging biomarker assessment of a cervical lesion (eg, cardiac pacemaker; ferromagnetic metal implant preventing safe imaging; obesity exceeding device limits;

DCE/DW-MRI imaging not indicated; history of severe MRI contrast allergy; or renal impairment that would put the subject at risk of nephrogenic systemic fibrosis)

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator or subinvestigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment but can continue the study observations and examinations, the subject will complete protocol-specified off-treatment visits and procedures. In Part 2, the subject who discontinues study treatment will complete survival follow-up unless the subject withdraws consent. For subjects who discontinues study treatment due to reasons other than disease progression, the scheduled tumor assessments will be performed continuously until disease progression, other anticancer treatment is started, or death, whichever comes first. If a subject withdraws consent, the date will be documented in the source documents.

9.3.3.1 Discontinuation Criteria by Subject

If a subject meets any of the following criteria, the investigator or subinvestigator will discontinue treating the subject with study treatment.

1. The subject refuses to continue participation in the study or wished to withdraw consent.
2. Major violations (eg, violations of the inclusion or exclusion criteria) are found after study enrollment, and they significantly affect the primary endpoint and subject safety.
3. The subject is unable to continue the study due to an AE in the opinion of the investigator or subinvestigator.
4. The subject becomes pregnant.
5. Progressive disease (When the investigator or subinvestigator judges clinical benefit of E7130 is maintained, it can be continued after discussion with the sponsor.)
6. When the dose of E7130 needs to be reduced to less than the starting dose (25 $\mu g/m^2$) in Part 1 and less than the minimum dose specified in Part 2 due to the development of a drug-related AE.
7. The investigator or subinvestigator thinks that discontinuation of the study is appropriate.

9.4 Treatment

9.4.1 Treatment Administered

9.4.1.1 Treatment administered (Part 1)

In Part 1, E7130 will be administered as an every-2-week/3-week IV infusion. The study drug that will be used is 0.05 and 0.25 mg/mL vials. The initial dose level of E7130 will be 25 $\mu g/m^2$ with the every-2-week regimen. Dose escalation of the every-2-week regimen, and

the initial dose and dose escalation of the every-3-week regimen are provided in "9.1.1.4 Dose escalation and dose assignment of subjects."

Refer to the following for preparation of E7130 with normal saline and infusion time, which depend on the magnitude of dose level. The subject's condition should be carefully monitored during the infusion of E7130. Appropriate actions will be taken in case of any abnormal findings. If no clinically significant AEs related to the study treatment occur during Cycle 1, the infusion time of the study drug can be halved in Cycle 2 and beyond (eg, when it is ≥60 minutes, ≥30 minutes). The investigator or subinvestigator should carefully monitor the condition of subjects after the modification.

- 25 μg/m^2 : IV infusion over ≥5 minutes
- >25 - 33 μg/m^2 : IV infusion over ≥7 minutes
- >33 - 50 μg/m^2 : IV infusion over ≥10 minutes
- >50 - 100 μg/m^2 : IV infusion over ≥15 minutes
- >100 - 180 μg/m^2 : IV infusion over ≥30 minutes
- >180 - 1800 μg/m^2 : IV infusion over ≥60 minutes
- >1800 μg/m^2 : IV infusion over ≥120 minutes

(*): Refer to the manual provided by the sponsor concerning the dilution concentration, administration equipment (syringe, drip bag, etc.) according to the doses.

Body surface area for each subject will be computed based on height and weight at Screening or Baseline to calculate the amount of study treatment (μg/body) for each subject. In the event of a >10% change in body weight, the amount of study treatment (μg/body) will be recalculated.

When intravenous indwelling catheter is used, E7130 should be administered via a different lumen for blood collection, if possible. E7130 should be administered via the most distal lumen of the multi-lumen catheter to prevent drug concentration analyses from confounding.

9.4.1.2 Dose interruption, skip and Dose reduction for toxicity (Part 1)

1. Cycle 1

- If DLT occurs:
  E7130 will be interrupted/skipped immediately. When the investigator or subinvestigator judges it clinically appropriate, the next scheduled administration can be done at a reduced 1 dose level lower after toxicity is recovered to Grade ≤1 or baseline Grade as Cycle 2 Day 1 (C2D1). If the investigator or subinvestigator determines that no dose reduction is necessary, a decision will be made after prior consultation with the sponsor.
- If no DLT occurs:
  E7130 will not be interrupted/skipped as a rule until DLT is observed.
  When the investigator or subinvestigator judges it clinically appropriate during E7130 administration, E7130 can be interrupted or skipped and resumed at the same dose level

at any time. The next scheduled administration can be done at the same dose level. Dose reduction cannot be permitted.

2. Cycle 2 or later

The criteria for initiation and dose reduction of E7130 treatment, shown below, shall be followed when any E7130-related toxicity occurs.

Criteria for treatment initiation (Part 1)

E7130 will be administered when the subjects meet all of the following treatment criteria. For subjects who have not yet recovered from E7130-related toxicities to the following criteria, the next scheduled Cycle Day 1 may be postponed for up to 14 days for recovery from the toxicities. In addition, subjects who cannot receive the next scheduled Cycle Day 1 of E7130 due to holidays, public holidays etc., regardless of disease conditions, may receive the administration up to 7 days after the scheduled date. Further postponement if necessary will be determined in consultation with the sponsor.

- Neutrophil count $\geq 1.0\times10^3/\mu L$.
- Platelet count $\geq 7.5\times10^4/\mu L$.
- Non-hematological toxicity recovered to Grade 0 to 2 (excluding non-clinically significant laboratory abnormalities).

For subjects who cannot receive the study drug on Day 15 due to reasons such as E7130-related toxicities after Cycle 3 in the every-2-week regimen, the next scheduled day of Day 15 may be postponed for up to 7 days. When the scheduled administration date of Day 15 is postponed, E7130 administration on Day 1 of the next cycle must be NO SOONER than 14 days later from the actual administration day. In this case, the examination scheduled for Day 22 will be conducted 7 days after the actual administration day.

Criteria for dose reduction (Part 1)

If hematological toxicity or non-hematological toxicity of the same severity as that specified by the DLT criteria (see Section 9.5.1.5.7) occurs, the subsequent doses of E7130 will be administered at a one level lower dose. The dose to be reduced will be determined by the investigator and sponsor based on the safety data available. If the investigator or subinvestigator determines that no dose reduction is necessary, a decision will be made after prior consultation with the sponsor. If a toxicity requiring to postpone study drug administration occurs, the next dose may be reduced by one level at the discretion of the investigator or subinvestigator. If a dose reduction is required for other reasons, a decision will be made in consultation with the sponsor. Once the dose is reduced, it cannot be increased at a later date.

[Added in the protocol version 6]

9.4.1.3 Treatment administered (Part 2)

The study drug that will be used in Part 2 is the 0.25 mg/mL vial. E7130 will be administered at a dose of 480 $\mu g/m^2$ over 60 minutes (approximate) as an every-3-week IV

infusion. E7130 will be administered at a dose of 410 μg/m^2 over 60 minutes (approximate) as an every-3-week IV infusion because the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks based on the safety results of 480 μg/m^2 obtained from the first 8 subjects in Part 2 since the protocol version 8. If the starting dose is changed to 350 μg/m^2, E7130 will be administered over 60 minutes (approximate) as an every-3-week IV infusion. If no clinically significant AEs related to the study treatment occur during the first infusion of the study drug, the infusion time of the study drug can be changed to ≥30 minutes (approximate) in Cycle 2 and beyond. The investigator or subinvestigator should carefully monitor the condition of subjects if the infusion time is changed.

Body surface area for each subject will be computed based on height and weight at Screening or Baseline to calculate the amount of study treatment (μg/body) for each subject. In the event of a >10% change in body weight, the amount of study treatment (μg/body) will be recalculated. If the dose of E7130 is reduced, the dose of E7130 (μg/body) may be reconsidered based on the body surface area.

9.4.1.4 Dose interruption, skip and Dose reduction for toxicity (Part 2)

The criteria for initiation and dose reduction of E7130 treatment, shown below, shall be followed when any E7130-related toxicity occurs.

Criteria for treatment initiation (Part 2)

E7130 will be administered when the subjects meet all of the following treatment criteria. For subjects who have not yet recovered from E7130 related toxicities to the following criteria, the next scheduled Cycle Day 1 may be postponed for recovery from the toxicities. For subjects who cannot receive the next scheduled Cycle Day 1 of E7130 due to other reasons such as holidays, public holidays etc., the next scheduled day of administration may be postponed. If treatment is postponed for >21 days, resumption should be discussed with the sponsor. If the treatment cannot be resumed more than 21 days after the scheduled start date of the next cycle, discontinuation of the study should be considered.

- Neutrophil count ≥1.0×10^3/μL.
- Platelet count ≥7.5×10^4/μL.
- Non-hematological toxicity recovered to Grade 0 to tolerable 2 (excluding non-clinically significant laboratory abnormalities).

Criteria for dose reduction (Part 2)

If any of the following toxicities occurs, the dose of E7130 will be administered at a one level lower dose. The dose should be reduced in the order of 480, 410, 350, and then 300 μg/m^2, and if a further dose reduction is necessary, the study should be discontinued as a rule. The dose should be reduced in the order of 410, 350, 300 and then 250 μg/m^2, and if a further dose reduction is required, the study should be discontinued as a rule because the regimen and dose to be used in Part 2 were changed to 410 μg/m^2 every 3 weeks based on the safety results of 480 μg/m^2 obtained from the first 8 subjects in Part 2 since the protocol version 8. If the starting dose is changed to 350 μg/m^2, the dose should be reduced in the

order of 350, 300, 250 and then 200 μg/m^2, and if a further dose reduction is necessary, the study should be discontinued as a rule. If the investigator or subinvestigator determines it beneficial for the subject to continue the study with a further dose reduction, a decision will be made after consultation with the sponsor. If the investigator or subinvestigator determines that no dose reduction is necessary, a decision will be made after prior consultation with the sponsor. If a dose reduction is required for reasons other than the following toxicities, a decision will be made in consultation with the sponsor. Once the dose is reduced, it cannot be increased at a later date.

Starting dose: 410 μg/m^2→350 μg/m^2→300 μg/m^2→250 μg/m^2→ study discontinuation
Starting dose: 350 μg/m^2→300 μg/m^2→250 μg/m^2→200 μg/m^2→study discontinuation

Hematological toxicity	
- Grade 4 neutropenia persisting for ≥7 days[a] - Grade 3 – 4 febrile neutropenia[a] - Grade 4 thrombocytopenia or Grade 3 thrombocytopenia that requires blood transfusion - Grade 4 anemia, or anemia that requires blood transfusion	If the event occurred in the previous cycle, the dose should be reduced in the next cycle.
Non-hematological toxicityb:	
- Grade 4 - Grade 3 [c] - Intolerable Grade 2[d]	If the event occurred in the previous cycle, the dose should be reduced in the next cycle.
a: If these toxicities occur without prophylactic treatment, the next cycle dose may not be reduced with effective prophylactic treatment. Discuss and agree with the investigator, sponsor, and medical expert in advance. b: Excluding Grade3 - 4 laboratory abnormalities that are not clinically significant or recovered to Grade 0 - 2 without treatment c: Excluding any events which can be managed and controlled to Grade 2 or less by maximal medical management. d: Tolerability of Grade 2 events will be decided by the investigator or subinvestigator.	

9.4.1.5 Actions to be taken for peripheral sensory neuropathy and hyponatremia caused by E7130

In the 410 μg/m^2 and 480 μg/m^2 every-3-week groups in Part 2, Grade 3 to 4 peripheral sensory neuropathy and hyponatremia occurred, which might lead to dose interruption/reduction/discontinuation of the study drug. If peripheral sensory neuropathy or hyponatraemia occurred, appropriate measures should be taken in reference to the following.

1. Implementation of medically appropriate measures from the initial stage of onset (including Grade 1)

   [Example]

[Peripheral sensory neuropathy]

- Compliance with "9.4.1.4 Dose interruption, skip and Dose reduction for toxicity (Part 2)"; Early postponement and dose reduction should be considered based on the subject's condition.

[Hyponatremia]

- Compliance with "9.4.1.4 Dose interruption, skip and Dose reduction for toxicity (Part 2)";
- Treatment tailored to root cause, use of oral NaCl (if root cause is difficult to identify), etc.

2. Consultation with specialists

9.4.1.6 Other Considerations

In the non-clinical study of E7130, there are no findings suggesting increased QT interval, but it has been reported that the QT interval increased after treatment with eribulin that is a synthetic analog of E7130. In this study, as shown in the Schedule of Procedures/Assessments (Table 13,Table 14,Table 15), subjects will undergo electrocardiogram (ECG) and electrolyte tests (blood chemistry) before the first dose as well as during the treatment with E7130 to carefully monitor the subjects' condition. Appropriate actions will be taken in case of any abnormal findings.

9.4.2 Identity of Investigational Product

E7130 will be supplied by the sponsor in labeled containers.

E7130 is a clear solution for intravenous administration. The 0.05 mg/mL formulation contains 0.05 mg of E7130 drug substance, sodium chloride, sodium dihydrogenphosphate, and sodium hydroxide in 1 mL solution. The 0.25 mg/mL formulation contains 0.25 mg of E7130 drug substance, sodium chloride, trometamol and hydrochloric acid in 1 mL solution.

Details of preparation and dosing of E7130 will be provided in a separate manual.

9.4.2.1 Chemical name, etc., of E7130

Test drug code: E7130

Chemical name (IUPAC):	(1"*S*,2*R*,2'*S*,3"*S*,3a'*S*,4*S*,4a*S*,6*R*,6"*S*,7*R*,7'*S*,7a'*S*,8a*S*,9"*S*,12"*S*,14"*R*,16"*R*,18"*S*,20"*S*,22"*R*,26"*R*,28"*S*,29"*S*,30"*R*,34"*R*,37"*S*,39"*R*,40"*S*,41"*R*,43"*R*,44"*S*)-6-(Aminomethyl)-7-hydroxy-4,7',14",29"-tetramethyl-8",15"-dimethylidenedecahydro-3*H*,3'*H*,32"*H*-dispiro[pyrano[3,2-*b*]pyran-2,5'-furo[3,2-*b*]pyran-2',24"-[2,19,23,27,31,38,42,45,47,48,49]undecaoxaundecacyclo[32.9.2.1^{3,40}.1^{3,41}.1^{6,9}.1^{12,16}.0^{18,30}.0^{20,28}.0^{22,26}.0^{37,44}.0^{39,43}]nonatetracontan]-32"-one

Molecular formula: $C_{58}H_{83}NO_{17}$

Molecular weight: 1066.29

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

The following information has to be provided:

- For clinical study use only
- Name and address of the sponsor
- Drug identifier
- Batch number (lot number)
- Storage conditions, expiration date

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The head of the medical institution is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means , such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent and satisfy all eligibility requirements (see Section 9.3) will receive E7130. There is no randomization in this study.

1. The investigator, subinvestigator, or clinical research coordinator will issue the Subject ID Number identified by the sponsor to individual subjects who provide signed informed consent for study entry and record it in “Subject Screening Log.”
2. The investigator, subinvestigator, or clinical research coordinator will screen the subjects and determine subject eligibility based on the inclusion and exclusion criteria. The investigator, subinvestigator, or clinical research coordinator will record the decision on the subject eligibility in the “Subject Screening Log.”
3. The investigator, subinvestigator, or clinical research coordinator will notify the sponsor of Subject ID Number, date of informed consent, and eligibility decision by email or fax immediately after the investigator or subinvestigator determines the subject eligibility.
4. After confirming the subject eligibility, the sponsor will inform the investigator, subinvestigator, or clinical research coordinator of the date of registration confirmed, dose cohort, and dose to be administered, by email or fax (subject registration to study).

5. The investigator or subinvestigator will confirm the subject registration and then confirm the subject eligibility based on the results of baseline assessments according to the inclusion and exclusion criteria. After that, the investigator or subinvestigator will initiate study drug administration.

9.4.4 Selection of Doses in the Study

The rationale for the selection of the doses in the study is provided in "Section 7.3.2 Rationale for Choice of Starting Dose" and "Section 7.3.5 Rationale for the Method of Deciding the Dose of the Next Dose Group."

9.4.5 Selection and Timing of Dose for Each Subject

The selection and timing of the dose for each subject are provided in "9.4.1 Treatment Administered."

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy other than drugs administered to the subject beginning from the time the subject signs the study ICF until the last observation will be recorded on the case report form (CRF). For all drugs, the name, dose/frequency (excluding patches), treatment start dates (or timing of starting treatment), treatment end dates, and reason for use will be recorded on the CRF. Concomitant drugs such as premedications, diagnostic agents, solutions, or fluid transfusions provided for surgery, medical examinations, or administrations will be excepted. For concomitant therapy, the name, treatment start dates (or timing of starting treatment), treatment end dates, and reason for use will be recorded on the CRF. For subjects who will discontinue the study at Screening, prior and concomitant therapies will not be recorded on the CRF.

9.4.7.1 Drug-Drug Interactions

Risks of drug-drug interactions, which E7130 alter the PK of other drugs, would be low based on the data of nonclinical studies.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

The following concomitant therapies and drugs will be prohibited.

1. Cycle 1 (Part 1 only)

   Treatments (*), changes in doses, and changes in drugs for the purpose to prevent DLT occurrence.

   (*) Prophylaxis treatment of nosocomial infection, acceptable treatment in DLT criteria (see "9.5.1.5.7 Definition Of Dose-Limiting Toxicity") or continuous treatment for

complication is permitted ensuring that concomitant treatment should be kept to a minimum during this study. And unless the purpose to prevent DLT, G-CSF or equivalent may be used at the discretion of the investigator or subinvestigator in accordance with institutional or national guidelines.

2. From the start of the first dose of study drug to the time of study drug discontinuation (refer to Inclusion Criteria 8).
    1. Treatments for malignant tumors other than E7130 such as surgery, chemotherapy, hormone therapy, and immunotherapy.
    2. Radiotherapy: However, palliative radiotherapy for bone metastasis of painful non-target lesions is allowed up to 2 lesions. Palliative radiotherapy is permitted only after completion of DLT assessment in Part 1.
    3. Other investigational drugs
3. Cycle 1 and 2 (Part 1 only)
   Inhibitor of P-glycoprotein (P-gp) (refer to the Attachment separately provided to each site)

Note: Concomitant use of drugs that inhibit P-gp should be avoided if possible from 14 days before C1D1 to 14 days after the last dose of study drug. If concomitant use of drugs that inhibit P-gp is necessary during this period, the sponsor and medical expert should be contacted in advance (other than the prohibited concomitant period in Part 1 and Part 2).

If subjects receive additional antitumor therapies, such as surgical therapy, chemotherapy, radiotherapy, hormone therapy, palliative radiotherapy, or immunotherapy, this will be judged to represent evidence of disease progression, and study medication will be discontinued.

9.4.8 Treatment Compliance

The investigator, subinvestigator, or clinical research coordinator will record the treatment compliance. The clinical research associate (CRA) will review the treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

The assigned pharmacist (or the designee) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator or subinvestigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The assigned pharmacist (or the designee) must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, unused study drugs that are returned by the subjects (unused study drug-1), unused study drugs that are

shipped to site but not dispensed to subjects (unused study drug-2), and return of reconciled study drugs to the sponsor (a sum of unused study drugs 1 and 2) or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) documentation of returns to the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a CRA or a representative of a health authority. Upon completion of unused drug accountability procedures and documentation of study drugs return by the assigned pharmacist (or designee), all unused study drugs are to be returned to the sponsor. Unused study drugs that are returned from the site are hand-delivered to CRAs and to be returned to the sponsor's designated depot.

Drug accountability will be reviewed by the CRA during site visits and at the completion of the study, and throughout the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes Subject ID Number, date of written informed consent, age, sex, race, and ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History And Current Medical Conditions

Medical and surgical history and current medical conditions will be recorded at the Screening. All medical and surgical history that is considered to have effects on safety, efficacy, or PK by the investigator or subinvestigator and medical conditions that are identified at Screening must be noted on the CRF.

The following information on primary disease and its prior therapies will be collected at Screening and noted on the CRF.

1. First tumor diagnosis (date of diagnosis, name of diagnosis, diagnostic method [histology/cytology], histological type, staging [eg, TNM classification]), known genetic mutation, and diagnostic information related to protein overexpression
2. For subjects with breast cancer (BC), status of HER2 expression, and sensitivity to hormones (estrogen receptor [ER], progesterone receptor [PR])
3. For subjects with squamous cell carcinoma of the head and neck (SCCHN) (oropharynx), infection of human papillomavirus (HPV)
4. For subjects with gastric cancer [GC], status of HER2 expression

5. For subjects with colorectal cancer [CRC], KRAS, NRAS, or BRAF mutation
6. Prior therapies for primary disease
    1. Surgical therapy (date, surgical procedure)
    2. Radiotherapy (site of radiotherapy, end date of radiotherapy)
    3. Chemotherapy (name of medication, type of therapy, best overall response [if available], initial dose, total dose [anthracycline treatment only], start/end date of medication
    4. Other anti-cancer procedure (procedure name, start/end date of procedure)
7. In Cohort 1 (SCCHN) in Part 2, the presence/absence of HPV infection, PD-L1 expression status, and smoking history
8. In Cohort 2 (UC) in Part 2, the presence or absence of FGFR mutation, PD-L1 expression status

9.5.1.2.2 HEIGHT

Height (cm) will be measured at Screening only.

9.5.1.2.3 VIRUS TEST

Hepatitis B surface (HBs) antigen, HBs antibody, hepatitis B virus core (HBc) antibody, hepatitis C virus (HCV) antibody, and HIV antibody tests will be performed at Screening. Subject who are anti-HBs/HBcAb (+) with less than 20 IU/mL HBV-DNA are eligible for this study. Subject who are HCV antibody (+) are eligible for the study if they are HCV-RNA (-).

If data of a viral test conducted 6 months before the first dose of E7130 is available, it can be used as the data for the screening test.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 TUMOR ASSESSMENT

Tumor assessment (target lesion, non-target lesion, and presence or absence of new lesion) will be performed based on RECIST 1.1 (see Appendix 3) by the investigator or subinvestigator with appropriate devices such as CT and MRI. In Part 1, tumor assessments will be implemented at screening and every 6 weeks (±7 days) from C1D1 through week 24 (6, 12, 18, and 24 weeks), then every 12 weeks (±7 days) (eg, 36, 48, 60… weeks after C1D1) thereafter and at discontinuation, or in a timely manner if disease progression is clinically indicated. In Part 2, tumor assessments will be carried out at screening and every 6 weeks (±7 days) from C1D1, at discontinuation, or in a timely manner if disease progression is clinically indicated. Tumor assessments will be based on images acquired by the same imaging modality (eg, CT, MRI) and under the same operating conditions as the screening scan. In Part 2, subjects going off treatment without disease progression will also undergo tumor assessments every 6 weeks (±7 days) from C1D1 through Week 24 (6, 12, 18 and 24

weeks), then every 12 weeks (±7 days) thereafter until disease progression, initiation of another anticancer therapy, death, or cutoff date whichever comes first.

If necessary, the investigator, subinvestigator, or study coordinator will provide the sponsor with duplicates or digital copies of images used as the source of the tumor assessment.

To ensure comparability throughout the study, it is critical that the same image modality, methodology and scan acquisition technique is applied, and contrast is consistently provided unless IV contrast becomes medically contraindicated during the course of treatment or the dose of contrast needs to be adjusted based on the subject's health status.

9.5.1.3.2 IMAGING MODALITY FOR EACH BODY SITE

The recommended imaging modality for each body site is described below. Chest x-ray will not be used in assessment of target lesions.

- Brain: CT or MRI
- Chest: CT
- Abdomen: CT or MRI
- Pelvis: CT or MRI
- Bone: Bone scintigraphy or whole body MRI (at screening), CT or MRI
- Other sites: CT, MRI, etc.
- Clinical lesions that can be inspected macroscopically or by palpation: Clinical assessment

1. CT or MRI

Subjects, except, for example, oral or IV contrast media are medically contraindicated will undergo CT or MRI scans with contrast. Subjects with an allergy to contrast, etc., will be assessed with non-contrast CT for chest and MRI of abdomen and pelvis. In Part 2, if there is any concern about the imaging method described above, the imaging method will be determined after discussion among the investigator, sponsor, and medical expert.

Attenuation correction CT portions or ultrasonography will not be employed for tumor assessment. And low dose CT portions of a combined positron emission tomography (PET)-CT also will not be employed for tumor assessment.

1. At screening

- Chest, abdomen, pelvis, and any other known or suspected sites of disease will be assessed.
- Data before obtaining informed consent can be used if the data obtained within 28 days before the first dose of study drug.

2. During the Treatment Phase, at discontinuation, or if clinical indicated

- Chest, abdomen, pelvis, and any other known or suspected sites of disease will be assessed.

- Data within 28 days before discontinuation date when investigator or subinvestigator judges, if available, can be used as the discontinuation data.

2. Brain scan

In Part 1, a brain scan (CT with contrast or MRI pre- and post-gadolinium) must be performed at screening to assess potential central nervous system (CNS) disease and/or metastases. Subjects with an allergy to contrast will be assessed with non-contrast MRI. At screening, data within 28 days before the first dose of E7130 can be used (data before obtaining informed consent can be used). For subjects with previously treated eligible brain metastases, a brain scan must be conducted at all tumor assessment time points. Screening is not mandatory in Part 2.

3. Bone scan

When bone lesions are suspected, bone scans (^{99}m-technetium polyphosphonate scintigraphy, whole body bone MRI, or ^{18}F-NaF-PET) will be carried out at screening, every 24 weeks from C1D1 and as clinically indicated. At screening, data within 28 days before the first dose of E7130 can be used (data before obtaining informed consent can be used). For the follow-up of non-target bone lesions, the use of MRI or CT is recommended. For bone lesions that can be followed-up with bone scan only, the bone scan will be assessed every 24 weeks (±14 days) from C1D1, or sooner if clinically indicated.

During the period when bone scan is not required, any response other than "not evaluable (NE)" may be assigned at each time point, even if the subject is not evaluable at the time point. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure compatibility unless contraindications to tracer develop.

4. Clinical Assessment

For lesions that can be inspected macroscopically, it will be recommended to use color images including a ruler (scale) so that the size of the lesion can be assessed. For lesions that can be inspected by palpation, the size of the lesion will be clinically assessed, and recorded in the source document. When skin lesions are recorded in the form of color digital images, a millimeter ruler and a label indicating the Subject ID number and date will be included with each image. In addition, a caliper will be used for measurement.

9.5.1.3.3 TUMOR MARKER

The investigator or subinvestigator will identify tumor markers likely to be appropriate for the primary disease if applicable. The identified tumor markers will be measured at the same timing as the tumor assessments.

Measurement results of the identified tumor markers will be recorded on the CRF.

9.5.1.3.4 SURVIVAL FOLLOW-UP (PART 2 ONLY)

In the follow-up for OS in Part 2, the subject's survival and post-anti-cancer treatment after discontinuation of treatment with E7130 will be followed every 6 months (approximate) from

the last observation and if requested by the sponsor up to 18 months after the enrollment of the last subject, and the information will be recorded on the CRF. If a subject cannot visit the study site, it will be permitted to collect follow-up information by telephone or e-mail.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

9.5.1.4.1.1 PLASMA AND URINE CONCENTRATIONS OF E7130

Plasma concentrations of E7130 will be measured to evaluate the PK for all subjects enrolled in Part 1 or Part 2. In the every-2-week regimen of Part 1, urine samples will be collected at predose on C1D1, and then 6-hour urine collection will be done from the start of infusion to 6 hours post-infusion until development of the first DLT. In cohorts after development of the first DLT, urine samples will be collected at predose on C1D1, and then 24-hour urine collection will be done from the start of infusion to 24 hours post-infusion to evaluate urine concentrations of E7130. If it is judged that sufficient data has been obtained, the 24-hour urine collection will be discontinued.

Detailed blood and urine sampling schedules for PK assessment of E7130 are shown in Table 3 (every-2-week regimen in Part 1), Table 6 (every-3-week regimen in Part 1), Table 7 (Part 2) and Table 4/Table 5. See the manual for a description of collection, handling, and shipping procedures for PK samples. When 12-lead ECGs for repolarization assessment are to be monitored concurrently with blood collections for PK assessment, the 12-lead ECGs will be performed before the blood collections. In case of using a multi-lumen catheter, samples must be taken "upstream" or proximally and not taken from the same lumen used for study drug administration. If PK blood sampling and Holter ECG recording are performed at the same time points in Part 2, the PK blood samples will be collected immediately after the subject has rested in a supine position for 15 minutes (about 10 minutes of rest, 5-minute extraction window) for Holter ECG recording. In case the study drug is IV administered via peripheral vein, samples must not be taken from the same arm receiving the study drug.

Concentrations of E7130 in plasma and urine will be quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) methodology using a previously validated assay.

For PK assessment, actual time and date of blood and urine samplings; and starting time of urine collection (defined as the starting time of infusion of study drug on C1D1) and ending time of urine collection will be recorded on the CRF. Actual starting time and ending time of infusion of E7130, date of infusion, and dose of E7130 will be recorded on the CRF.

Table 3 Blood Sampling Schedule for Pharmacokinetic Assessments in Part 1 (every 2 weeks) – All Subjects

E7130 and Metabolite

Day	Sampling time	Additional sampling point[a]		
		Infusion time 30 minutes	**Infusion time 60 minutes**	**Infusion time 120 minutes**
C1D1	Predose	–	–	–
	–	15 minutes after start of infusion	–	–
	–	–	20 minutes after start of infusion	–
	–	–	45 minutes after start of infusion	45 minutes after start of infusion
	–	–	–	90 minutes after start of infusion
	End of infusion	–	–	–
	20 minutes post-infusion	–	–	–
	40 minutes post-infusion	–	–	–
	1 hour post-infusion	–	–	–
	2 hours post-infusion	–	–	–
	4 hours post-infusion	–	–	–
	6 hours post-infusion	–	–	–
C1D2	24 hours post-infusion	–	–	–
C1D3	48 hours post-infusion	–	–	–
C1D8	168 hours post-infusion	–	–	–
C1D15	Predose (However, when infusion on C1D15 is skipped, the samples should be collected as those at 336 hours post-infusion on C1D1.)	–	–	–
	–	15 minutes after start of infusion	–	–
	–	–	20 minutes after start of infusion	–
	–	–	45 minutes after start of infusion	45 minutes after start of infusion
	–	–	–	90 minutes after start of infusion
	End of infusion	–	–	–

Table 3 Blood Sampling Schedule for Pharmacokinetic Assessments in Part 1 (every 2 weeks) – All Subjects

E7130 and Metabolite

Day	Sampling time	Additional sampling point[a]		
		Infusion time 30 minutes	**Infusion time 60 minutes**	**Infusion time 120 minutes**
C1D22 [7 days after infusion on Day 15]	168 hours post-infusion	–	–	–
C2D1	Predose	–	–	–
	–	15 minutes after start of infusion	–	–
	–	–	20 minutes after start of infusion	–
	–	–	45 minutes after start of infusion	45 minutes after start of infusion
	–	–	–	90 minutes after start of infusion
	End of infusion	–	–	–
	20 minutes post-infusion	–	–	–
	40 minutes post-infusion	–	–	–
	1 hour post-infusion	–	–	–
	2 hours post-infusion	–	–	–
	4 hours post-infusion	–	–	–
	6 hours post-infusion	–	–	–
C2D2	24 hours post-infusion	–	–	–
C2D3	48 hours post-infusion	–	–	–
C2D8	168 hours post-infusion	–	–	–
C2D15	Predose	–	–	–
	–	15 minutes after start of infusion	–	–
	–	–	20 minutes after start of infusion	–
	–	–	45 minutes after start of infusion	45 minutes after start of infusion
	–	–	–	90 minutes after start of infusion
	End of infusion	–	–	–
C2D22 [7 days after infusion on Day 15]	168 hours post-infusion	–	–	–
C3D1	Predose	–	–	–
	End of infusion	–	–	–

Table 3 Blood Sampling Schedule for Pharmacokinetic Assessments in Part 1 (every 2 weeks) – All Subjects

E7130 and Metabolite

Day	Sampling time	Additional sampling point[a]		
		Infusion time 30 minutes	Infusion time 60 minutes	Infusion time 120 minutes
C3D8 (when subjects visit the site)	Not determined	–	–	–
C3D15	Predose	–	–	–
	End of infusion	–	–	–
C4D1	Predose	–	–	–
	End of infusion	–	–	–
C4D8 (when subjects visit the site)	Not determined	–	–	–
C4D15	Predose	–	–	–
	End of infusion	–	–	–
C5D1	Predose	–	–	–
	End of infusion	–	–	–
C6D1	Predose	–	–	–
	End of infusion	–	–	–
C7D1	Predose	–	–	–
	End of infusion	–	–	–
C8D1	Predose	–	–	–
	End of infusion	–	–	–
Discontinuation[b]	Not determined	–	–	–

Sampling points for PK might be changed based on PK data.
C#D# = Cycle # Day #, PK = pharmacokinetics.
a: In case infusion time is 30 or more minutes, sampling points will be added depending on infusion time.
b: Blood collection is not required after the 36th cycle. [Added in Version 11]

Table 4 Urine Sampling Schedule for Pharmacokinetic Assessments in Part 1 (every 2 weeks) – Cohorts Until Development of First DLT

E7130 and Metabolite

Day	Sampling time
C1D1	Predose (urine sampling)
	Start of infusion to 6 hours post-infusion (urine collection)

C#D# = Cycle # Day #, DLT = dose-limiting toxicity.

Table 5 Urine Sampling Schedule for Pharmacokinetic Assessments in Part 1 (every 2 weeks) – Cohorts After Development of First DLT

E7130 and Metabolite

Day	Sampling time
C1D1	Predose (urine sampling)
C1D1, C1D2	Start of infusion to 6 hours post-infusion (urine collection)
	6 to 12 hours post-infusion (urine collection)
	12 to 24 hours post-infusion (urine collection)

C#D# = Cycle # Day #, DLT = dose-limiting toxicity.

Table 6 Blood Sampling Schedule for Pharmacokinetic Assessments in Part 1 (every 3 weeks) – All Subjects

E7130 and Metabolite

Day	Sampling time	Additional sampling point[a]		
		Infusion time 30 minutes	**Infusion time 60 minutes**	**Infusion time 120 minutes**
C1D1	Predose	–	–	–
	–	15 minutes after start of infusion	–	–
	–	–	20 minutes after start of infusion	–
	–	–	45 minutes after start of infusion	45 minutes after start of infusion
	–	–	–	90 minutes after start of infusion
	End of infusion	–	–	–
	20 minutes post-infusion	–	–	–
	40 minutes post-infusion	–	–	–
	1 hour post-infusion	–	–	–
	2 hours post-infusion	–	–	–
	4 hours post-infusion	–	–	–
	6 hours post-infusion	–	–	–
C1D2	24 hours post-infusion	–	–	–
C1D3	48 hours post-infusion	–	–	–
C1D8	168 hours post-infusion	–	–	–
C1D15	336 hours post-infusion	–	–	–
C2D1	Predose	–	–	–
	–	15 minutes after start of infusion	–	–
	–	–	20 minutes after start of infusion	–
	–	–	45 minutes after start of infusion	45 minutes after start of infusion
	–	–	–	90 minutes after start of infusion
	End of infusion	–	–	–
	20 minutes post-infusion	–	–	–
	40 minutes post-infusion	–	–	–
	1 hour post-infusion	–	–	–
	2 hours post-infusion	–	–	–
	4 hours post-infusion	–	–	–
	6 hours post-infusion	–	–	–
C2D2	24 hours post-infusion	–	–	–
C2D3	48 hours post-infusion	–	–	–
C2D8	168 hours post-infusion	–	–	–
C2D15	336 hours post-infusion	–	–	–
C3D1	Predose	–	–	–
	End of infusion	–	–	–
C3D8 (when subjects visit the site)	Not determined	–	–	–
C3D15	336 hours post-infusion	–	–	–
C4D1	Predose	–	–	–
	End of infusion	–	–	–
C4D8 (when subjects visit the site)	Not determined	–	–	–
C4D15	336 hours post-infusion	–	–	–
C5D1	Predose	–	–	–

Table 6 Blood Sampling Schedule for Pharmacokinetic Assessments in Part 1 (every 3 weeks) – All Subjects

E7130 and Metabolite

Day	Sampling time	Additional sampling point[a]		
		Infusion time 30 minutes	Infusion time 60 minutes	Infusion time 120 minutes
	End of infusion	–	–	–
C5D15	336 hours post-infusion	–	–	–
C6D1	Predose	–	–	–
	End of infusion	–	–	–
C6D15	336 hours post-infusion	–	–	–
C7D1	Predose	–	–	–
	End of infusion	–	–	–
C7D15	336 hours post-infusion	–	–	–
C8D1	Predose	–	–	–
	End of infusion	–	–	–
C8D15	336 hours post-infusion	–	–	–
Discontinuation	Not determined	–	–	–

Sampling points for PK might be changed based on PK data.
C#D# = Cycle # Day #, PK = pharmacokinetics.
a: In case infusion time is 30 or more minutes, sampling points will be added depending on infusion time.

Table 7 CCI [redacted]

CCI [redacted]

9.5.1.4.1.2 CCI [redacted]

CCI [redacted]

9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, And Other Biomarker, Assessments

If a mechanism of action of E7130 is made cleared in preclinical studies, additional biomarkers may be measured and analyzed. The objectives of biomarker measurement are the identification of factors that predict or determine clinical response to E7130, or that may be used to understand the pharmacology of E7130 in an individual. In addition, samples obtained may be used for the development of E7130 diagnostic agents etc. These analyses will be reported as a separate report. See Appendix 6 for a description of security, use, and retention of the samples as well as subject privacy for PD, PGx, and other biomarker research.

9.5.1.4.2.1 Blood Biomarker

Blood samples for biomarker measurements will be obtained from all subjects enrolled in the study. Biomarkers such as TGF-β1 and VEGF, etc., will be measured (but not limited to these).

Blood sampling schedules for blood biomarker assessments are shown in Table 8 (every-2-week regimen in Part 1), Table 9 (every-3-week regimen in Part 1) and Table 10 (Part 2). Blood biomarkers will be measured using previously validated assays. See the manual for a description of collection, handling, and shipping procedures for biomarker samples.

For biomarker assessment, actual time and date of blood will be recorded on the CRF.

Table 8 Blood Sampling Schedule for Blood Biomarker Assessments in Part 1 (every 2 weeks) – All Subjects

Day	Sampling time
C1D1	Predose
C1D2	24 hours post-infusion
C1D3	48 hours post-infusion
C1D8	168 hours post-infusion
C1D15	Predose (However, when infusion on C1D1 15 is skipped, the samples should be collected as those at 336 hours post-infusion on C1D1.)
C1D22 [7 days after infusion on Day 15]	168 hours post-infusion
C2D1	Predose
C3D1	Predose
Discontinuation[a]	–

C#D# = Cycle # Day #.
a: Blood collection is not required after the 36th cycle. [Added in Version 11]

Table 9 Blood Sampling Schedule for Blood Biomarker Assessments in Part 1 (every 3 weeks) – All Subjects

Day	Sampling time
C1D1	Predose
C1D2	24 hours post-infusion
C1D3	48 hours post-infusion
C1D8	168 hours post-infusion
C1D15	336 hours post-infusion
C2D1	Predose
C3D1	Predose
Discontinuation	–

C#D# = Cycle # Day #.

Table 10 Blood Sampling Schedule for Blood Biomarker Assessments in Part 2– All Subjects

Day	Sampling time
C1D1	Predose
C1D8	168 hours post-infusion
C1D15	336 hours post-infusion
C2D1	Predose
C2D8	168 hours post-infusion
C2D15	336 hours post-infusion
C3D1,C4D1,C5D1,C6D1	Predose
C3D8,C4D8,C5D8,C6D8	168 hours post-infusion
D8 after C7 and subsequent cycles	168 hours post-infusion
Discontinuation	–

C#D# = Cycle # Day #.

9.5.1.4.2.2 TUMOR TISSUE BIOMARKER

Archival or biopsy tissues will be collected, and CD31, α-SMA positive CAF, etc., (but not limited to these) will be measured as biomarkers.

In Part 1, pre-treatment archival or biopsy tissues will be collected from all subjects enrolled in the study. (The pre-treatment biopsy tissues may also serve as the pre-treatment archival tissues. PGx is optional.)

In Part 2, biopsy tissues will be collected as follows:

- Cohort 1 (SCCHN): Pre- and post-treatment (screening, C2D3 to C2D9) tissues will be collected from all subjects. This does not apply to cases where it is found difficult to perform biopsy at pre- and post-treatment after informed consent. Subjects must have consented to PGx. If a subject withdraws from the study prior to the post-treatment biopsy, a biopsy may be taken during the Follow-up Phase instead of a post-treatment biopsy. The investigator or subinvestigator should consider prophylactic use of G-CSF for pre- and post-treatment biopsies. If tissue samples cannot be obtained between C2D3 and C2D9 for safety reasons, etc., the investigator or subinvestigator should examine to

carry out a biopsy between Days 3 and 9 of the next or subsequent cycle. In addition, the sponsor may request the subjects to provide pre-treatment archival tumor tissues if any.

- Cohort 2 (UC): Pre-treatment archival or biopsy tissues will be collected from all subjects (The pre-treatment biopsy tissues may also serve as the pre-treatment archival tissues). PGx is optional.

See the manual for a description of collection, handling, and shipping procedures for tumor tissue biomarker samples.

9.5.1.4.2.3 IMAGING BIOMARKERS (PART 2, COHORT 1 ONLY)

DCE-MRI and DW-MRI assess changes of tumor blood flow. Biomarkers may include K^{trans}, V_e, K_{ep}, and ADC (but not limited to these). Part 2, Cohort 1 (SCCHN): DCE-MRI and DW-MRI will be performed at pre- and post-treatment (screening, C2D3 to C2D22) in all subjects. This does not apply to cases where it is found difficult to implement them after informed consent. Post-treatment assessments are recommended to be conducted between C2D8 and C2D15. If a subject is withdrawn from the study before DCE-MRI and DW-MRI at post-treatment, they can be performed during the Follow-up Phase instead of those at post-treatment. When there is only one lesion appropriate for DCE-MRI, DW-MRI and biopsy, and the same lesion will be used for the DCE-MRI and DW-MRI and biopsy, in principle, the biopsy should be implemented after DCE-MRI and DW-MRI at each time point, and DCE-MRI and DW-MRI should be carried out at least 3 weeks after the previous biopsy.

If DCE-MRI or DW-MRI cannot be performed between C2D3 and C2D22 for safety reasons, etc., the investigator or subinvestigator should consider implementing them between Days 3 and 22 of the next or subsequent cycle. However, if the same lesion is used for DCE-MRI, DW-MRI and biopsy, DCE-MRI and DW-MRI should be conducted at least 3 weeks after the previous biopsy.

In Cohort 2, DCE-MRI and DW-MRI will not be carried out.

The measurement data will be sent to the central laboratory for analysis. Refer to the separately provided manual for lesions suitable for imaging biomarker measurements, conditions, and procedure.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades (for both increasing and decreasing severity), and serious adverse events (SAEs); laboratory evaluation for hematology, blood chemistry, blood coagulation, and urinalysis; measurement of vital signs, arterial oxygen saturation, body weight, and 12-lead ECGs, ECOG PS; and performance of physical examinations.

In addition, DLTs will be assessed to determine MTD in Part 1.

9.5.1.5.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug(s) is E7130.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE).
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in a change in treatment, or discontinuation of study drug.
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline).
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last observation. SAEs that occur by the last observation will also be collected.

All abnormal laboratory values assessed as AEs will be recorded in the CRF. Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator and subinvestigator to review all laboratory values to determine if an abnormal laboratory value is considered an AE. Medical and scientific judgment should be exercised in deciding whether an abnormal laboratory finding should be considered an independent AE.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 msec and there is an increase of more than 60 msec from baseline. Any ECG abnormality that the investigator or subinvestigator considers as an AE should be reported as such.

All AEs must be followed until the last observation (ic, for 30 days after the subject's last dose), or until resolution, whichever comes first. If a new anticancer agent needs to be immediately started due to deterioration in the subject's condition, the last observation visit can be conducted before 30 days after the last dose of the study drug has passed but prior to starting the new anticancer agent. However, Grade 2 or higher peripheral sensory neuropathy occurred in the 350 μg/m^2 every-3-week group will be followed up until resolution, starting a new anticancer agent, or the end of the survival follow-up, whichever occurs first, if possible. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator or subinvestigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v4.03. Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

- Items to be considered when assessing the relationship of an AE to the study treatment are:
- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related)	A causal relationship between the study drug and the AE is a reasonable possibility.
No (not related)	A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Events associated with special situations include pregnancy or exposure to the study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error (see Sections 9.5.4.2 and 9.5.4.3). These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no “adverse event” (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, blood coagulation test, and urinalysis, are summarized in (Table 11). The Schedule of Procedures/Assessments (Table 13 [Part 1 (every 2 weeks)], Table 14[Part 1 (every 3

weeks)]), and Table 15 [Part 2]) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. Clinical laboratory tests will be performed at each site.

Table 11 Clinical Laboratory Tests

Category	Parameters
Hematology	RBC count, hemoglobin, hematocrit, platelets, and WBC count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Liver function tests	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (γ-GTP), total bilirubin, direct bilirubin
Renal function tests	Blood urea nitrogen (BUN), creatinine
Other	Glucose[a], albumin, cholesterol, triglycerides, lactate dehydrogenase (LDH), total protein, uric acid, amylase, lipase, sodium, potassium, chloride, calcium, phosphorus, CRP
Blood coagulation tests	Activated partial thromboplastin time (aPTT)
Urinalysis	pH, protein, glucose, occult blood, sodium[b], osmotic pressure[b], creatinine[c], β2 microglobulin[c], N-acetylglucosaminidase (NAG)[c]

ALP = alkaline phosphatase, ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CRP = C-reactive protein, γ-GTP = gamma glutamyltransferase, LDH = lactate dehydrogenase.
a: At screening, sample is taken on fasted condition. After that, samples are taken on fasted condition whenever possible.
b: The items will be tested only in Part 2.
c: The items will be tested only in the 350 μg/m^2 every-3-week group in Part 2.

All hematology, blood chemistry, blood coagulation test, and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle. Refer to criteria for E7130 dose interruption/skip/dose reduction in Sections 9.4.1.2 and 9.4.1.4 for the management of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the CRF.

9.5.1.5.4 Vital Signs, Arterial Oxygen Saturation, And Weight Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), transcutaneous measurement of arterial oxygen saturation (%), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 13 [Part 1 (every 2 weeks)], Table 14 [Part 1 (every 3 weeks)]), and Table 15 [Part 2] by a validated method. Blood pressure and pulse will be measured after the subject has rested.

When vital signs are to be monitored concurrently with blood collections, vital sign measurements will be performed at least 10 minutes apart (approximate).

9.5.1.5.5 PHYSICAL EXAMINATION

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 13 [Part 1 (every 2 weeks)], Table 14 [Part 1 (every 3 weeks)], and Table 15 [Part 2]). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 complexes derived simultaneously from each lead should be used for the assessment. ECGs will be obtained after the subject has rested.

When 12-lead ECGs are to be monitored concurrently with blood collections, 12-lead ECG recording will be performed prior to blood collections.

9.5.1.5.6.1 TWELVE-LEAD ELECTROCARDIOGRAM FOR SAFETY ASSESSMENT

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 13 [Part 1 (every 2 weeks)], Table 14 [Part 1 (every 3 weeks)], and Table 15 [Part 2]).

Twelve-lead ECGs for safety assessment will be monitored at end of infusion , and can be covered by 12-lead ECGs for [redacted] in the next section (Section 9.5.1.5.6.2) at 10 minutes post-infusion of Baseline (Day –7 to Day –1), Cycles 1 and 2 in Part 1. In these cases, 3 records of ECGs will be performed. When ECGs for [redacted] is not substituted, consideration of ECG abnormality and measurement of QTcF may be performed from 1 record of ECGs.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the ECG abnormality will be recorded on the CRF.

9.5.1.5.6.2 TWELVE-LEAD ELECTROCARDIOGRAM FOR [redacted]

Twelve-lead ECGs will be recorded at the point described in Table 12 from all subjects in Part 1 to investigate the effect of E7130 on [redacted]. At each time point, 3 records of ECGs will be performed. Subjects should be in the recumbent position from 10 minutes prior to starting of the ECG recording to the end of the recording. In Part 2, 12-lead ECGs will be recorded in all subjects using a Holter device on C1D1. The detailed

measurement time points are presented in Table 7. If PK blood sampling and Holter ECG recording after the start of E7130 infusion are performed at the same time points, the PK blood samples will be collected immediately after the subject has rested in a supine position for 15 minutes (about 10 minutes of rest, 5-minute extraction window) for Holter ECG recording.

These 12-lead ECGs data will be transferred to central laboratory for CCI [redacted]

Table 12 Recording Schedule for 12-lead Electrocardiogram for Ventricular Repolarization Assessment in Part 1 (every 2 weeks, every 3 weeks) – All Subjects

Day	Recording time
Baseline (Day –7 to Day –1)	Predose
	10 minutes post-infusion
	2 hours post-infusion
	4 hours post-infusion
C1D1	Predose
	10 minutes post-infusion
	2 hours post-infusion
	4 hours post-infusion
C1D2	24 hours post-infusion
C2D1	Predose
	10 minutes post-infusion
	2 hours post-infusion
	4 hours post-infusion
C2D2	24 hours post-infusion

C#D# = Cycle # Day #.

9.5.1.5.7 Definition Of Dose-Limiting Toxicity (Part 1)

DLTs will be assessed to determine MTD.

The following toxicities developed in Cycle 1 and the causal relationship with E7130 cannot be ruled out are regarded as "DLT." The decision on DLT will be made by the investigator, sponsor, and medical expert after discussion. If necessary, the suggestions from independent medical advisors may be sought for this purpose.

a. Febrile neutropenia
b. Grade 4 neutropenia that persists for more than 7 days or that requires hematopoietic stimulating agents.
c. Grade 4 thrombocytopenia or thrombocytopenia that requires platelet transfusion.
d. Grade 4 anemia, or anemia that requires red blood cell transfusion.

e. Any Grade 3 non-hematological toxicity with the exception of:
   - Abnormal clinical laboratory values with no clinical significance
   - Any events which can be managed and controlled to Grade 2 or less by maximal medical management.

f. Any Grade 4 non-hematological toxicity

g. (For the every-2-week regimen only) Development of any toxicity that is considered to be related to E7130 and where the dose was skipped on C1D15. However, when dose skip on C1D15 is required for reasons other than the following toxicities, this will not be deemed as a DLT. In this situation, the relevant subject will be excluded from assessments of DLT and new subjects will be added.
   - Neutrophil count $<1.0\times10^3/\mu L$.
   - Platelet count $<7.5\times10^4/\mu L$.
   - Intolerable Grade 2 or 3 non-hematological toxicity (excluding non-clinically significant laboratory abnormalities).

h. (For the every-3-week regimen only) Development of any toxicity that is considered to be related to E7130 and where the dose at C2D1 needs to be postponed for over 14 days for recovery from the toxicities. However, when dose postponement on C2D1 is required for reasons other than toxicity, this will not be regarded as a DLT.

9.5.1.5.8 Determination Of Maximum Tolerated Dose (MTD) (Part 1)

A dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate for each dose will be defined as the MTD. Toxicity data up to Cycle 2 are taken into account to finally determine the MTD.

9.5.1.5.9 Other Safety Assessments

9.5.1.5.9.1 ECOG-PS

ECOG-PS will be assessed as designated in the Schedule of Procedures/Assessments (Table 13[Part 1 (every 2 weeks)], Table 14 [Part 1 (every 3 weeks)], and Table 15 [Part 2]).

9.5.1.5.9.2 Pregnancy Test

An hCG or β-hCG test will be performed for women of childbearing potential. A serum or urine sample will be taken at visits as designated in the Schedule of Procedures/Assessments (Table 13 [Part 1 (every 2 weeks)], Table 14 [Part 1 (every 3 weeks), and [Part 2]).

All females will be considered to be of childbearing potential unless:

- Postmenopausal (amenorrheic for at least 12 consecutive months without other known or suspected cause)
- Sterilized surgically (bilateral tubal ligation at least 1 month before dosing, total hysterectomy, or bilateral oophorectomy at least 1 month before dosing)

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 13, Table 14 and Table 15 present the schedule of procedures/assessments for every-2-week regimen and every-3-week regimen in Part 1, and Part 2, respectively.

Table 13 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 1 (every 2 weeks)

Phase	Pretreatment Phase			Treatment Phase											Follow-Up Phase	
Period	Informed consent	Screening	Baseline[e]	Cycle 1 & 2 (28 days/cycle)							Cycle 3 or later (28 days/cycle)				Discontinuation	Last observation[r]
Day		–28 to –1	–3 to –1	1[x]	2	3	5	8 (±1)	15 (±2)[w]	22 [7 days post-infusion on Day 15] (±1)	1[x]	8[l] (±3)	15[z] (±2)	22[l,z] (±3)	Date of discontinuation (+7 days)	30 days after last administration (+7)
Informed consent	X[a]			X[a]												
Inclusion/ exclusion		X	X													
Demographic data, Prior medications, Medical history/complication		X														
Height		X[c]														
Weight[b]		X	X	X[o]							X[s]				X[p]	
Vital signs Transcutaneous measurement of arterial oxygen saturation		X	X	X[i,o]				X	X	X	X[i,s]	X	X	X	X[p]	X
Physical examination		X	X	X[o]				X	X	X	X[s]	X	X	X	X[p]	X
ECOG-PS		X	X	X[o]				X	X	X	X[s]	X	X	X	X[p]	
12-lead ECG for safety assessment		X[f]		X[f,i]					X[f]		X[i]				X[p]	
12-lead ECG for repolarization assessment			X[g]	X[g,i]	X[g,i]											
Urinalysis		X	X	X[o]				X	X	X	X[s]	X	X	X	X[p]	X
Hematology Blood chemistry Blood coagulation tests		X	X	X[o]				X	X	X	X[s]	X	X	X	X[p]	X
Virus test		X[c]														
Pregnancy[y] (only if applicable)		X	X													X
Tumor assessment: CT/MRI		X[d]		X[m]											X[q]	
Brain scan		X		X[u]												
Bone scan		X		X[v]												
Tumor marker		X[d]		X[m]											X[q]	

Table 13 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 1 (every 2 weeks)

Phase		Pretreatment Phase			Treatment Phase											Follow-Up Phase	
Period		Informed consent	Screening	Baseline[e]	Cycle 1 & 2 (28 days/cycle)							Cycle 3 or later (28 days/cycle)				Discontinuation	Last observation[r]
Day			–28 to –1	–3 to –1	1[x]	2	3	5	8 (±1)	15 (±2)[w]	22 [7 days post-infusion on Day 15] (±1)	1[x]	8[l] (±3)	15[z] (±2)	22[l,z] (±3)	Date of discontinuation (+7 days)	30 days after last administration (+7)
PK	Blood				X[h,i]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[n,i]	X[n]	X[n]		X[h]	
	Urine[t]				X	←	—	—	—	→							
Blood biomarker					X[j]	X[j]	X[j]		X[j]	X[j]	X[j]	X[j]				X[j]	
PGx (tissue)			X														
Archival tissues		X[k]															
E7130 administration					X					X		X		X			
Adverse event		←	—	—	—	—	—	—	—	—	—	—	—	—	→		
Concomitant medications /therapies		←	—	—	—	—	—	—	—	—	—	—	—	—	→		

The day of actual first dose is counted as Day 1 of the cycle which is followed by the subsequent schedule.
BC = breast cancer, C#D# = Cycle # Day #, CT = computerized tomography, ECOG-PS = Eastern Cooperative Oncology Group-Performance Status, MRI = magnetic resonance imaging, NE = not evaluable, PET = positron emission tomography, PGx = pharmacogenomics, PK = pharmacokinetics.

[a] Informed consent should be obtained before initiating the study and, for the continuation of Cycle 2 or later administration, informed consent should be obtained before initiating the study or before entering Cycle 2.

[b] Body weight will be measured during Screening, baseline, prior to E7130 administration on Day 1 of Cycle 2 onward, and at the discontinuation. E7130 dose should be modified if the subject experiences a >10% change in body weight.

[c] Height will be collected during Screening only. If data of a viral test conducted 6 months before the first dose of E7130 is available, it can be used as the data for the screening test.

[d] Data within 28 days before the first dose of E7130 can be used (Data before obtaining informed consent can be used).

[e] Regarding tests which are performed in both screening and baseline, if screening test is done within 3 days before first dose of E7130, baseline tests do not have to be done.

[f] Twelve-lead ECGs for safety assessment will be monitored at end of infusion, and can be covered by 12-lead ECGs for repolarization assessment at 10 min post-infusion between baseline (Day –7 to Day –1) and Cycles 1 to 2.

[g] Twelve-lead ECGs for repolarization assessment will be monitored at predose, 10 min, 2, 4 and 24 h post-infusion on Day 1 of Cycles 1 and 2. Within 7 days prior to C1D1, 12-lead ECGs will be monitored at the same time points (predose, 10 min, 2, and 4 h post-infusion) as scheduled on C1D1 (4 points/Day).

[h] Blood collection for E7130 concentration at predose, end of infusion, 20 and 40 min, 1, 2, 4, 6, 24, 48, and 168 hours post-infusion on C1D1 and C2D1, at pre-dose, end of infusion and 168 hours post-infusion on C1D15 and C2D15 and at discontinuation. Blood collection for E7130 concentration at 15 minutes after the start of the infusion (if infusion is 30 minutes), at 20 and 45 minutes after the start of the infusion (if infusion is 60 minutes), and at 45 and 90 minutes after the start of the infusion (if infusion is 120 min) on C1D1, C1D15, C2D1 and C2D15. Blood collection at discontinuation is not required after the 36th cycle. [Added in Version 11]

[i] When vital signs or 12-lead ECGs are to be monitored concurrently with blood collections, vital sign measurements/12-lead ECG recording will be performed prior to blood collections.

Table 13 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 1 (every 2 weeks)

Phase	Pretreatment Phase			Treatment Phase											Follow-Up Phase	
Period	Informed consent	Screening	Baseline[e]	Cycle 1 & 2 (28 days/cycle)							Cycle 3 or later (28 days/cycle)				Discontinuation	Last observation[r]
Day		–28 to –1	–3 to –1	1[x]	2	3	5	8 (±1)	15 (±2)[w]	22 [7 days post-infusion on Day 15] (±1)	1[x]	8[l] (±3)	15[z] (±2)	22[l,z] (±3)	Date of discontinuation (+7 days)	30 days after last administration (+7)

[j] Blood collection for biomarker assessment at predose, 24, 48 and 168 hours post-infusion on C1D1, and at predose and 168 hours post-infusion on C1D15. After Cycle 2, blood collection at predose on Day 1 until a completion of Cycle 3. Blood collection at discontinuation is not required after the 36th cycle. [Added in Version 11]

[k] As pretreatment sample, archival or biopsy tissues will be collected (mandatory).

[l] Cycle 3 or later, visits can be omitted only when the investigator or subinvestigator judges that the subject's safety is ensured.

[m] Tumor assessments will be performed based on RECIST 1.1. Tumor assessments will be carried out during the Pretreatment phase and then every 6 weeks (±7 days) for the first 24 weeks (counting from C1D1), then every 12 weeks (±7 days) (eg, 36, 48, 60… weeks after C1D1), or at appropriate timing (Part 1) and additional timing (Part 2) if disease progression is clinically indicated. CT scans (with oral and intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to C1D1), using the above tumor assessment schedule, and as clinically indicated. MRI scans may be used instead of CT scans for abdomen and pelvis and other areas of disease except for chest; however, chest must be assessed using CT. Chest disease may not be followed using chest x-ray. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be performed without IV contrast. The same method of assessment must be used at all-time points as used at Screening.

[n] Blood collection at pre-dose and end of infusion on C3D1, C3D15, C4D1 and C4D15, and (when subjects visit the site), C3D8 and C4D8, and pre-dose and end of infusion on C5D1, C6D1, C7D1 and C8D1 (Sampling points for PK might be changed based on PK data).

[o] At predose of E7130 infusion on C2D1 only. If the study infusion on C2D1 is postponed, it should also be done on C1D29.

[p] Data within 7 days before discontinuation date when investigator or subinvestigator judges, if available, can be used as the discontinuation data.

[q] Data within 28 days before discontinuation date when investigator or subinvestigator judges, if available, can be used as the discontinuation data.

[r] SAEs, regardless of causality assessment, must be collected until the last observation (ie, 30 days after the last dose of the study drug). If a new anticancer agent needs to be immediately started due to deterioration in the subject's condition, the last observation visit can be conducted before 30 days after the last dose of the study drug has passed but prior to starting the new anticancer agent.

[s] At predose of E7130 infusion. Data within 2 days before the study drug administration can be allowed.

[t] At predose and 0 to 6-hour urine collection of subjects on C1D1 until development of first DLT in Part 1. At predose and 0 to 24-hour urine collection of subjects on C1D1 in cohorts after development of first DLT in Part 1.

[u] Screening brain scans will be performed by MRI pre- and post- gadolinium or CT with contrast enhancement, within 28 days prior to C1D1. For subjects with history of treated brain metastases, brain scans will be performed at every tumor assessment time point. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure compatibility.

[v] A bone scan (99m-technetium polysphosphonate scintigraphy, whole body bone MRI, or 18F-NaF-PET) will be performed at Screening when bone lesions are suspected and then every 24 weeks (within the 24th week ±2 weeks) in conjunction from C1D1 when positive at Screening, or sooner if clinically indicated. Subjects with disease present in the breast are required to have a bone scan performed at Screening and every 24 weeks thereafter. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure compatibility. If a non-target bone lesion is being followed by bone scan (not present on CT/MRI), and is not imaged at a follow-up time point because a bone scan is not required at that time point, the time point non-target lesion response will be based on the other non-target lesions and will not be considered not evaluable (NE).

[w] The tests on Day 15 of Cycles 1 and 2 will be performed on the day of E7130 infusion.

Table 13 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 1 (every 2 weeks)

Phase	Pretreatment Phase			Treatment Phase											Follow-Up Phase	
Period	Informed consent	Screening	Baseline[e]	Cycle 1 & 2 (28 days/cycle)							Cycle 3 or later (28 days/cycle)				Discontinuation	Last observation[r]
Day		–28 to –1	–3 to –1	1 [x]	2	3	5	8 (±1)	15 (±2)[w]	22 [7 days post-infusion on Day 15] (±1)	1 [x]	8 [l] (±3)	15[z] (±2)	22 [l z] (±3)	Date of discontinuation (+7 days)	30 days after last administration (+7)

[x] For subjects who have not yet recovered from E7130 related toxicities, the next scheduled Cycle Day 1 may be postponed for up to 14 days for recovery from the toxicities. In addition, subjects who cannot receive the next scheduled Cycle Day 1 of E7130 due to holidays, public holidays etc., regardless of disease conditions, may receive the administration up to 7 days after the scheduled date.

[y] A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 3 days before the first dose of study drug.

[z] For subjects who have not yet recovered from E7130-related toxicities after Cycle 3, the next scheduled day of Day 15 may be postponed for up to 7 days. When the scheduled administration date of Day 15 is postponed, E7130 administration on Day 1 of the next cycle must be NO SOONER than 14 days later from the actual administration day. In this case, the examination scheduled for Day 22 will be conducted 7 days after the actual administration day.

Table 14 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 1 (every 3 weeks)

Phase	Pretreatment Phase			Treatment Phase									Follow-Up Phase	
Period	Informed consent	Screening	Baseline[e]	Cycle 1 & 2 (21 days/cycle)						Cycle 3 or later (21 days/cycle)			Discontinuation	Last observation[q]
Day		–28 to –1	–3 to –1	1[w]	2	3	5	8 (±1)[v]	15 (±1)[v]	1[w]	8[k] (±3)	15 (±3)	Date of discontinuation (+7)	30 days after last administration (+7)
Informed consent	X[a]			X[a]										
Inclusion/ exclusion		X	X											
Demographic data, Prior medications, Medical history/complication		X												
Height		X[c]												
Weight[b]		X	X	X[s]						X[r]			X[o]	
Vital signs Transcutaneous measurement of arterial oxygen saturation		X	X	X[s,n]				X	X	X[r,n]	X	X	X[o]	X
Physical examination		X	X	X[s]				X	X	X[r]	X	X	X[o]	X
ECOG-PS		X	X	X[s]				X	X	X[r]	X	X	X[o]	
12-lead ECG for safety assessment		X[f]		X[f,n]						X[n]			X[o]	
12-lead ECG for repolarization assessment			X[g]	X[g,n]	X[g,n]									
Urinalysis		X	X	X[s]				X	X	X[r]	X	X	X[o]	X
Hematology Blood chemistry Blood coagulation tests		X	X	X[s]				X	X	X[r]	X	X	X[o]	X
Virus test		X[c]												
Pregnancy[x] (only if applicable)		X	X											X
Tumor assessment: CT/MRI		X[d]		X[l]									X[p]	
Brain scan		X		X[t]										
Bone scan		X		X[u]										
Tumor marker		X[d]		X[l]									X[p]	
PK Blood				X[h,n]	X[h]	X[h]	X[h]	X[h]	X[h]	X[m,n]	X[m]	X[m]	X[h]	
PK Urine				X	←	—	—	→						

Table 14 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 1 (every 3 weeks)

Phase	Pretreatment Phase			Treatment Phase									Follow-Up Phase	
Period	Informed consent	Screening	Baseline[e]	Cycle 1 & 2 (21 days/cycle)						Cycle 3 or later (21 days/cycle)			Discontinuation	Last observation[q]
Day		–28 to –1	–3 to –1	1[w]	2	3	5	8 (±1)[v]	15 (±1)[v]	1[w]	8[k] (±3)	15 (±3)	Date of discontinuation (+7)	30 days after last administration (+7)
Blood biomarker				X[i]	X[i]	X[i]		X[i]	X[i]	X[i]			X	
PGx (tissue)		X												
Archival tissues	X[j]													
E7130 administration				X						X				
Adverse event	◄													►
Concomitant medications /therapies	◄													►

The day of actual first dose is counted as Day 1 of the cycle which is followed by the subsequent schedule.
BC = breast cancer, C#D# = Cycle # Day #, CT = computerized tomography, ECOG-PS = Eastern Cooperative Oncology Group-Performance Status, MRI = magnetic resonance imaging, NE = not evaluable, PET = positron emission tomography, PGx = pharmacogenomics, PK = pharmacokinetics.

[a] Informed consent should be obtained before initiating the study and, for the continuation of Cycle 2 or later administration, informed consent should be obtained before initiating the study or before entering Cycle 2.

[b] Body weight will be measured during Screening, baseline, prior to E7130 administration on Day 1 of Cycle 2 onward, and at the discontinuation. E7130 dose should be modified if the subject experiences a >10% change in body weight.

[c] Height will be collected during Screening only. If data of a viral test conducted 6 months before the first dose of E7130 is available, it can be used as the data for the screening test.

[d] Data within 28 days before the first dose of E7130 can be used (Data before obtaining informed consent can be used).

[e] Regarding tests which are performed in both screening and baseline, if screening test is done within 3 days before first dose of E7130, baseline tests do not have to be done.

[f] Twelve-lead ECGs for safety assessment will be monitored at end of infusion, and can be covered by 12-lead ECGs for repolarization assessment at 10 min post-infusion between baseline (Day –7 to Day –1) and Cycles 1 to 2.

[g] 12-lead ECGs will be monitored at predose, 10 min, 2, 4 and 24 h post-infusion on Day 1 of Cycles 1 and 2. Within 7 days prior to C1D1, 12-lead ECGs will be monitored at the same time points (predose, 10 min, 2, and 4 h post-infusion) as scheduled on C1D1 (4 points/Day).

[h] Blood collection for E7130 concentration at predose, end of infusion, 20 and 40 min, 1, 2, 4, 6, 24, 48, 168, and 336 hours post-infusion on C1D1 and C2D1 and at discontinuation. Blood collection for E7130 concentration at 15 minutes after the start of the infusion (if infusion is 30 minutes), at 20 and 45 minutes after the start of the infusion (if infusion is 60 minutes), and at 45 and 90 minutes after the start of the infusion (if infusion is 120 min) on C1D1 and C2D1.

[i] Blood collection for biomarker assessment at predose, 24, 48, 168, and 336 hours post-infusion on C1D1. After Cycle 2, blood collection at predose on Day 1 until a completion of Cycle 3.

[j] As pretreatment sample, archival or biopsy tissues will be collected (mandatory).

[k] Cycle 3 or later, visits can be omitted only when the investigator or subinvestigator judges that the subject's safety is ensured.

[l] Tumor assessments will be performed based on RECIST 1.1. Tumor assessments will be carried out during the Pretreatment phase and then every 6 weeks (±7 days) for the first 24 weeks (counting from C1D1), then every 12 weeks (±7 days) (eg, 36, 48, 60… weeks after C1D1), or at appropriate timing (Part 1) and additional timing (Part 2) if disease progression is clinically indicated. CT scans (with oral and intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to C1D1), using the above tumor assessment schedule, and as clinically indicated. MRI scans may be used instead of CT scans for abdomen and pelvis and other areas of disease except for chest; however, chest must be assessed using CT. Chest disease may not be followed using chest x-ray. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium

Table 14 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 1 (every 3 weeks)

Phase	Pretreatment Phase			Treatment Phase									Follow-Up Phase	
Period	Informed consent	Screening	Baseline[e]	Cycle 1 & 2 (21 days/cycle)						Cycle 3 or later (21 days/cycle)			Discontinuation	Last observation[q]
Day		–28 to –1	–3 to –1	1[w]	2	3	5	8 (±1)[v]	15 (±1)[v]	1[w]	8[k] (±3)	15 (±3)	Date of discontinuation (+7)	30 days after last administration (+7)

chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be performed without IV contrast. The same method of assessment must be used at all-time points as used at Screening.

m Blood collection at pre-dose, end of infusion, and 336 hours post-infusion on C3D1, C4D1, C5D1, C6D1, C7D1 and C8D1, and (when subjects visit the site) 3D8 and C4D8 (Sampling points for PK might be changed based on PK data).

n When vital signs or 12-lead ECGs are to be monitored concurrently with blood collections, vital sign measurements/12-lead ECG recording will be performed prior to blood collections.

o Data within 7 days before discontinuation date when investigator or subinvestigator judges, if available, can be used as the discontinuation data.

p Data within 28 days before discontinuation date when investigator or subinvestigator judges, if available, can be used as the discontinuation data.

q SAEs, regardless of causality assessment, must be collected until the last observation (ie, 30 days after the last dose of the study drug). If a new anticancer agent needs to be immediately started due to deterioration in the subject's condition, the last observation visit can be conducted before 30 days after the last dose of the study drug has passed but prior to starting the new anticancer agent.

r At predose of E7130 infusion. Data within 3 days before the study drug administration can be allowed.

s At predose of E7130 infusion on C2D1 only. If the study infusion on C2D1 is postponed, it should also be done on C1D22.

t Screening brain scans will be performed by MRI pre- and post- gadolinium or CT with contrast enhancement, within 28 days prior to C1D1. For subjects with history of treated brain metastases, brain scans will be performed at every tumor assessment time point. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure compatibility.

u A bone scan (99m-technetium polysphosphonate scintigraphy, whole body bone MRI, or 18F-NaF-PET) will be performed at Screening when bone lesions are suspected and then every 24 weeks (within the 24th week ±2 weeks) in conjunction from C1D1 when positive at Screening, or sooner if clinically indicated. Subjects with disease present in the breast are required to have a bone scan performed at Screening and every 24 weeks thereafter. The same methodology and acquisition techniques used at screening should be used throughout the study to ensure compatibility. If a non-target bone lesion is being followed by bone scan (not present on CT/MRI), and is not imaged at a follow-up time point because a bone scan is not required at that time point, the time point non-target lesion response will be based on the other non-target lesions and will not be considered not evaluable (NE).

v In Cycles 1and 2, Day 8 and 15 visit can have ±1 day allowance.

w For subjects who have not yet recovered from E7130 related toxicities, the next scheduled Cycle Day 1 may be postponed for up to 14 days for recovery from the toxicities. In addition, subjects who cannot receive the next scheduled Cycle Day 1 of E7130 due to holidays, public holidays etc., regardless of disease conditions, may receive the administration up to 7 days after the scheduled date.

x A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 3 days before the first dose of study drug.

Table 15 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 2

Phase	Pretreatment Phase			Treatment Phase										Follow-Up Phase	
Period	Informed consent	Screening	Baseline[d]	Cycle 1 (21 days/cycle)			Cycle 2 (21 days/cycle)				Cycle 3 or later (21 days/cycle)			Discontinuation	Last observation[m]
Day		−28 to 1	−3 to 1	1	8 (±1)	15 (±1)	1 (±1)	3	8 (±1)	15 (±1)	1 (±3)	8 (±3)	15[n] (±3)	Date of discontinuation (+7)	30 days after last administration (+7)
Informed consent	X[a]														
Inclusion/ exclusion		X	X												
Demographic data, Prior medications, Medical history/complication		X													
Height		X													
Weight[b]		X	X		X	X	X[e]		X	X	X[e]			X[k]	
Vital signs Transcutaneous measurement of arterial oxygen saturation		X	X		X	X	X[e]		X	X	X[e]	X	X	X[k]	X
Physical examination		X	X		X	X	X[e]		X	X	X[e]	X	X	X[k]	X
ECOG-PS		X	X		X	X	X[e]		X	X	X[e]	X	X	X[k]	
12-lead ECG for safety assessment		X					X[f]				X[f]			X[k]	
Holter ECG monitoring[q]				X											
Urinalysis		X	X		X	X	X[e]		X	X	X[e]	X	X	X[k]	X
Hematology Blood chemistry Blood coagulation tests		X	X		X	X	X[e]		X	X	X[e]	X	X	X[k]	X
Virus test[c]		X													
Pregnancy Test (only if applicable)		X	X												X
Tumor assessment: CT/MRI		X[g]			X[g]									X[l]	
Tumor marker		X[g]			X[g]									X[l]	
PK (blood)[h]				X	X	X	X		X	X	X	X[h]		X[k]	
Blood biomarker[i]				X	X	X	X		X	X	X	X[i]		X[k]	
Tumor sample/PGx[j]		X						X						X[r]	
Imaging biomarkers[o] (DCE-MRI, DW-MRI)		X						X						X[r]	
E7130 administration				X			X				X				
Adverse event[m]	◄														►

Table 15 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 2

Phase	Pretreatment Phase			Treatment Phase										Follow-Up Phase	
Period	Informed consent	Screening	Baseline[d]	Cycle 1 (21 days/cycle)			Cycle 2 (21 days/cycle)				Cycle 3 or later (21 days/cycle)			Discontinuation	Last observation[m]
Day		–28 to 1	–3 to 1	1	8 (±1)	15 (±1)	1 (±1)	3	8 (±1)	15 (±1)	1 (±3)	8 (±3)	15 [a] (±3)	Date of discontinuation (+7)	30 days after last administration (+7)
Concomitant medications /therapies	←														→
Survival survey															X [p]

The day of actual first dose is counted as Day 1 of the cycle which is followed by the subsequent schedule.
BC = breast cancer, C#D# = Cycle # Day #, CT = computerized tomography, ECOG-PS = Eastern Cooperative Oncology Group-Performance Status, MRI = magnetic resonance imaging, NE = not evaluable, PET = positron emission tomography, PGx = pharmacogenomics, PK = pharmacokinetics.

[a] Informed consent should be obtained before initiating the study.

[b] Body weight will be measured prior to E7130 administration. E7130 dose should be modified if the subject experiences a >10% change in body weight.

[c] If data of a viral test conducted 6 months before the first dose of E7130 is available, it can be used as the data for the screening test.

[d] Regarding tests which are performed in both screening and baseline, if screening test is done within 3 days before first dose of E7130, baseline tests do not have to be done.

[e] It will be performed prior to E7130 administration. Data within 1 day before the study drug administration in Cycle 2 within 3 days in Cycle 3 and subsequent cycles can be allowed.

[f] A 12 lead ECG (safety) will be carried out at the end of infusion.

[g] Tumor assessments will be performed based on RECIST 1.1. Data before obtaining informed consent can be used if the data obtained within 28 days before the first dose of study drug. Tumor assessments will be carried out during the Pretreatment phase and then every 6 weeks (±7 days) from C1D1, or as clinically indicated if necessary. CT scans (with oral and intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to C1D1), using the above tumor assessment schedule, and as clinically indicated. MRI scans may be used instead of CT scans for abdomen and pelvis and other areas of disease except for chest; however, chest must be assessed using CT. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, chest CT should be performed without IV contrast.

[h] Blood samples for measurement of E7130 concentrations will be collected as follows:
Cycle 1: Predose, 30 minutes after the start of the infusion, at the end of infusion, and 0.5, 1, and 3 to 5 hours, 168 hours (Day 8), and 336 hours (Day 15) post-infusion
Cycle 2: Predose, 15 minutes after the start of the infusion, at the end of infusion, and 0.5 and 168 hours (Day 8), and 336 hours (Day 15) post-infusion
Cycles 3 to 6: Predose, 15 minutes after the start of the infusion, at the end of infusion, and 168 hours (Day 8) post-infusion

[i] Blood sample will be collected on Days 1, 8 and 15 of Cycles 1 to 2, on Days 1 and Day 8 of Cycles 3 to 6, on Day 8 of Cycle 7 and thereafter, and at discontinuation. On Day 1, blood samples will be collected before study drug administration.

[j] Cohort 1 (SCCHN): Pre- and post-treatment (screening or baseline, C2D3 to C2D9) tissues will be collected from all subjects. It is recommended that pre-treatment biopsy be performed after eligibility is confirmed. Subjects must have consented to PGx. At the time of post-treatment biopsy, prophylactic administration of G-CSF should be considered based on the occurrence of toxicities.
Cohort 2 (UC): Pre-treatment archival or biopsy tissues will be collected from all subjects (The pre-treatment biopsy tissues may also serve as the pre-treatment archival tissues). PGx is optional.

[k] Data within 7 days before discontinuation date when investigator or subinvestigator judges, if available, can be used as the discontinuation data.

[l] Data within 28 days before discontinuation date when investigator or subinvestigator judges, if available, can be used as the discontinuation data.

[m] SAEs, regardless of causality assessment, must be collected until the last observation (ie, 30 days after the last dose of the study drug). If a new anticancer agent needs to be immediately started due to deterioration in the subject's condition, the last observation visit can be conducted before 30 days after the last dose of the study drug has passed but prior to starting the new anticancer agent.

Table 15 Schedule of Procedures/Assessments in Study E7130-J081-101: Part 2

Phase	Pretreatment Phase			Treatment Phase										Follow-Up Phase	
Period	Informed consent	Screening	Baseline[d]	Cycle 1 (21 days/cycle)			Cycle 2 (21 days/cycle)				Cycle 3 or later (21 days/cycle)			Discontinuation	Last observation[m]
Day		–28 to 1	–3 to 1	1	8 (±1)	15 (±1)	1 (±1)	3	8 (±1)	15 (±1)	1 (±3)	8 (±3)	15 [n] (±3)	Date of discontinuation (+7)	30 days after last administration (+7)

[n] Cycle 5 or later, visits can be omitted only when investigator or subinvestigator judges that the subject's safety is ensured.

[o] Cohort 1 (SCCHN) only. Pre- and post-treatment (screening or baseline, C2D3 to C2D22) tissues will be collected from all subjects. Refer to the separately provided manual for lesions suitable for imaging biomarker measurements, conditions, and procedure. It is recommended that pre-treatment tests are performed after eligibility is confirmed. It is recommended to implement the post-treatment tests between C2D8 and C2D15. The investigator or subinvestigator should determine the date of the test based on the occurrence of toxicities. When there is only one lesion appropriate for DCE-MRI, DW-MRI and biopsy, and the same lesion will be used for the DCE-MRI and DW-MRI and biopsy, in principle, the biopsy should be implemented after DCE-MRI and DW-MRI at each time point, and DCE-MRI and DW-MRI should be carried out at least 3 weeks after the previous biopsy.

[p] The subjects' survival and post-anti-cancer treatment after discontinuation of treatment with E7130 will be followed every 6 months (approximate) from the last observation and if requested by the sponsor up to 18 months after enrollment of the last subject.

[q] ECG will be performed using Holter ECG on C1D1. The 12-lead electrocardiogram [redacted] data will be extracted 3 times before infusion (eg, –45, –30 and –15 minutes), 30 minutes after the start of infusion, immediately before the end of infusion, 1 hour, and 3 to 5 hours post-infusion.

[r] If a subject is withdrawn from the study before biopsy, DCE-MRI and DW-MRI at post-treatment, biopsy, DCE-MRI and DW-MRI can be performed during the Follow-up Phase instead of biopsy, DCE-MRI and DW-MRI at post-treatment.

9.5.3 Appropriateness of Measurements

All clinical assessments were standard measurements commonly used in studies of solid tumor.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, blood coagulation tests, urinalysis, vital signs, transcutaneous measurement of arterial oxygen saturation, body weight, 12-lead ECGs, ECOG-PS, physical examinations, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported to the sponsor by email, etc., in principal, within 24 hours (no later than 1 calendar day) after obtaining the information. However, fatal events or life-threatening events must be reported immediately to the sponsor by telephone or other means before completing a SAE form, and the detail information should be reported to the sponsor on a completed SAE form no later than 1 business day after the first report.

SAEs, regardless of causality assessment, must be collected until the last observation. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator or subinvestigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Attachment separately provided to each site.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's or subinvestigator's assessment of causality.

Any relevant follow-up information received on SAEs should be forwarded from the investigator to the sponsor within 1 business day of its receipt. If the relevant follow-up information changes the assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 60 days of last study treatment, any partner's pregnancy of a male subject in which the estimated date of conception is either before the last visit or within 90 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 60 days of last study treatment, must be reported. The reporting period may be extended based on the half-life of E7130 calculated from this trial.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to the study drug through breastfeeding must be reported to the sponsor by email, etc., as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to the study drug through breastfeeding is provided in the Attachment. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting Of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, Or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol Intentional and inappropriate use of study drug not in accordance with the prescribed or authorized dose, route of administration, or indication(s) or use of prescription-only study drug without a prescription

Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the CRF.

9.5.4.3.2 Reporting Of Abnormal Hepatic Tests Of Clinical Interest

The following combination of abnormal laboratory tests*, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing and whether nonserious or serious, should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1). If the event does not meet serious criteria, the seriousness criteria on the SAE form should be indicated as "nonserious."

- Elevated AST or ALT laboratory value that is greater than or equal to 3× the upper limit of normal or if elevated greater than the upper limit of normal at baseline, then 3× the baseline for the subject
- Elevated total bilirubin laboratory value that is greater than or equal to 2× the upper limit of normal or if elevated greater than the upper limit of normal at baseline, then 1.5× the baseline for the subject
- Alkaline phosphatase laboratory value that is less than 2× the upper limit of normal

* These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require additional evaluation for an underlying etiology. In addition to reporting the abnormal hepatic laboratory tests on a SAE form, the site should also consult the medical monitor for guidance on assessment and follow-up. At a minimum, laboratory testing should be repeated at least once weekly until improvement or identification of a cause unrelated to study drug use that is unlikely to improve.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators, the head of the medical institution, and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described in the "Reporting of Serious Adverse Events" (see Section 9.5.4.1).

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor to regulatory authorities in compliance with regulatory requirements and established guidance. The format of these reports will be dictated by the regulatory requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 13 [Part 1 (every 2 weeks)], Table 14 [Part 1 (every 3 weeks)]).

The investigator or subinvestigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of primary reasons. Study disposition information will be collected on the CRF.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator, subinvestigator, or clinical research coordinator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator, subinvestigator, or clinical research will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator or subinvestigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by GCP, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of the sponsor and should not be made available in any form to third parties without written permission from the sponsor, except for authorized representatives of the sponsor or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed after the study data is cutoff or the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of the study data are described in this section. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP). The analysis plan will be finalized before database lock.

9.7.1.1 Statistical Design of Accelerated mTPI Method in Part 1

An accelerated mTPI design will be employed to determine the MTD of E7130. If drug-related Grade 2 or higher toxicity excluding clinically insignificant events is not observed in initial dosing cohort (3 subjects) of the every-2-week regimen, the dose will be escalated by single-subject DLT assessment in the following cohorts until drug-related Grade 2 or higher 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 3 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 3 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 the future dose level to be assigned, ie, dose escalation (E), staying at the current dose (S), or dose de-escalation (D), respectively.

This dose assignment rule minimizes the posterior expected penalty in the Bayes rule under a decision-theoretic framework with the equal prior expected penalties for E, S, and D. The entire dose assignment decision rule can be precalculated and presented.

The MTD will be determined when a prespecified maximum sample size, 7 or 5 cohorts being composed of 3 subjects for the every-2-week or every-3-week regimen, respectively (except for initial dosing cohort for the every-2-week 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, MTD may be determined early and then "Additional subjects to explore candidate OBD" may be enrolled.

The MTD is selected 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 up to Cycle 2 are taken into account to finally determine the 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) will be used to maintain monotonically increase of DLT rate with increasing dose level.

9.7.1.2 Study Endpoints

9.7.1.2.1 PRIMARY ENDPOINTS

Primary objective is to evaluate the tolerability and safety profile of E7130 in subjects with solid tumors.

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

9.7.1.2.2 SECONDARY ENDPOINTS

Secondary objectives are to determine the MTD of E7130, evaluate the PK of E7130 in plasma and urine, determine the RD for future studies, and assess the anti-tumor activity of E7130 in subjects with solid tumors. PFS and OS are also evaluated in Part 2 only.

- MTD determination: A dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate for each dose will be defined as the MTD. Toxicity data up to Cycle 2 are taken into account to finally determine the MTD.
- PK endpoints: PK parameters will be derived based on the plasma concentrations of E7130 using noncompartmental analysis (Part 1) and will include the following: 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 ($t_{½}$), total clearance (CL), and distribution volume (V_d). The amount of unchanged drug excreted in urine and renal clearance (CLR), if possible, will be derived in subjects who have urine samples in Part 1.
- RD determination: The RD is determined based on the MTD 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), ORR, DCR, CBR, DOR, PFS, OS and percent changes from baseline in the sum of the diameters of tumor target lesions (if applicable). BOR are 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. 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). PFS censoring rules will be detailed in the statistical analysis plan (SAP). DOR is defined as the time from the first documented date of PR or CR 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.

9.7.1.2.3 EXPLORATORY ENDPOINTS

CCI [redacted]

9.7.1.3 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 1PD and/or PGx data.

Tumor Tissue and Imaging Biomarker Analysis Set
is the group of subjects who received at least 1 dose of the study drug and had at least pre-treatment tissues or data.

9.7.1.4 Subject Disposition

Subjects who signed informed consent, and subjects who failed screening and the reason for screen failures will be presented. Subjects who were treated or not treated; and subjects who were ongoing or discontinued from study treatment and the reason for discontinuation will be presented.

9.7.1.5 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set will be summarized by each dose group and for total dose group in Part 1 and by dose group in each cancer cohort, cancer cohort, dose group, and for whole subjects in Part 2. Continuous demographic and baseline variables include age, height, and body weight ; categorical variables include sex, age group, race, ethnics, ECOG-PS, primary disease, and prior therapies for primary disease.

9.7.1.6 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) preferred name. Prior medications will be defined as medications that stopped before the first dose of study drug. When summarizing the data, concomitant medications will be defined as "medications that started before the first dose of study drug and were continuing at the time of the first dose of study drug" or "started on or after the date of the first dose of study drug until 30 days after the subject's last dose or until the subject initiates new anticancer therapy, whichever is earlier." All prior and concomitant medications will be presented in subject data listings.

9.7.1.7 Efficacy Analyses

Efficacy analyses will be conducted based on the Efficacy Analysis Set. In Part 1, the results will be summarized by each dose group, separately by regimen (every 2 weeks/every 3 weeks). In Part 2, the results will be summarized by dose group in each cancer cohort.

Part 1

Based on the tumor assessments according to RECIST 1.1, BOR will be summarized. If a subject has a BOR of non-CR/non-PD, the subject's BOR will be grouped with the SD category. ORR, DCR, CBR and its corresponding exact 2-sided 95% confidence intervals will be calculated.

Part 2

Besides the similar analyses for the Part 1, 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). The percent changes from baseline over time in the sum of the diameters of target lesions will be presented using spider plot. PFS, DOR and OS will also be summarized and plotted over time by Kaplan-Meier method. To summarize PFS and OS, estimates of median, Q1, Q3 and probabilities at 12 weeks and adequate time points, but are not limited to, will be used.

9.7.1.8 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.8.1 PHARMACOKINETIC ANALYSES

The PK analysis will be performed on the Pharmacokinetic Analysis Set.

In Part 1, 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. Urine concentrations of E7130 will be analyzed to determine the PK parameters including the amount of unchanged drug excreted in urine and renal clearance (CLR), if possible, in subjects who have urine samples in Part 1.

Plasma E7130 concentration data in Part 2 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.

9.7.1.8.2 Pharmacodynamic, Pharmacogenomic, And Other Biomarker Analyses

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

9.7.1.9 Safety Analyses

Tolerability analyses will be performed on the DLT Analysis Set. Safety analyses will be performed on the Safety Analysis Set.

In Part 1, tolerability analysis results will be summarized by each dose group.Safety analysis results will be summarized by each dose group and for total dose group, separately by regimen (every 2 weeks/every 3 weeks).

In Part 2, safety analysis results will be summarized by dose group in each cancer cohort, by cancer cohort, by dose group, and for whole subjects.

9.7.1.9.1 Extent Of Exposure

The number of cycles on treatment, the duration of treatment, the number of subject-month with study drug dosing, the number of study drug administered, total doses, dose intensity, and relative dose intensity will be summarized. The number of subjects requiring study drug dose reductions, interruption, and discontinuation will also be summarized.

9.7.1.9.2 Dose-Limiting Toxicity (DLT)

The number (percentage) of subjects with DLT will be summarized. DLT will also be summarized by type of toxicity. The estimates of DLT rate based on prior distribution of Bayesian statistics will be provided.

The MTD will be determined based on the DLTs and the method provided in Section 9.7.1.1.

9.7.1.9.3 Adverse Events

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

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges until 30 days after the subject's last dose, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

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

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

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with SAEs and TEAEs leading to death, discontinuation from study drug, study drug dose reduction or interruption will be summarized by SOC and PT. Subject data listings of all SAEs and AEs leading to death, discontinuation from study drug, study drug dose reduction or interruption will be provided.

9.7.1.9.4 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the last observation will be summarized by visit using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to the last observation will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

The CTCAE Grades at each visit and the highest postbaseline Grade will be summarized for those variables included in CTCAE v4.03. Changes from CTCAE grade at baseline to each postbaseline visit will be reported using shift tables.

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

Treatment-emergent markedly abnormal laboratory values (TEMAVs) will be identified based on CTCAE v4.03 as required.

9.7.1.9.5 VITAL SIGNS, ARTERIAL OXYGEN SATURATION, AND WEIGHT

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

9.7.1.9.6 ELECTROCARDIOGRAMS

ECG assessments were performed at each visit.

9.7.1.9.6.1 TWELVE-LEAD ELECTROCARDIOGRAM FOR SAFETY ASSESSMENT

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

In Part 2, descriptive statistics of measurements at each time point and their changes from baseline will be calculated in addition to the above.

The number (percentage) of subjects who met the following categories at least once after study drug administration will be calculated:

- QTcF interval >450 msec
- QTcF interval >480 msec
- QTcF interval >500 msec
- QTcF interval increases from baseline >30 msec
- QTcF interval increases from baseline >60 msec

9.7.1.9.6.2 TWELVE-LEAD ELECTROCARDIOGRAM FOR VENTRICULAR CCI [redacted]

CCI [redacted]

9.7.1.9.7 OTHER SAFETY ANALYSES

9.7.1.9.7.1 ECOG-PS

ECOG-PS will be summarized by scale at each visit and by the highest postbaseline scale.

9.7.1.10 Pharmacokinetic-Qt Interval Analyses

A plasma E7130 concentration-QTc analysis will be performed using 12-lead ECG data measured at the central laboratory. CCI [redacted]

9.7.2 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 the every-2-week regimen, if drug-related Grade 2 or higher toxicity is not observed in 3 subjects in the 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 the every-2-week 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 the every-3-week 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 in Part 2 will allow for further evaluation of safety and assessments of preliminary efficacy and biomarkers. The numbers of subjects were mainly based on the feasibility of enrollment. Cohort 1 will consist of 15 subjects with SCCHN, and Cohort 2 will include 16 subjects with UC. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2, approximately 20 subjects will be added to that dose level to further investigate safety and efficacy.

9.7.3 Interim Analysis

No interim analysis is planned for this study. DLTs will be assessed sequentially according to the dose escalation schedule. In Part 2, analyses may be performed for each cohort. If CR or PR is achieved in ≥2 of 10 subjects at the same dose level in Cohort 2 in Part 2, approximately 20 subjects will be added to that dose level. CR and PR require confirmation by the subsequent response assessment at 4 weeks or later.

Details of addition of subjects to Cohort 2 in Part 2 are as follows: Beta (1, 1) as a prior distribution will be used to estimate the posterior probability. After 10 subjects who received the same dose in the UC cohort are followed for a sufficient period, the addition or discontinuation of subjects will be determined using the posterior probability. The probability cut-off will be 60% and the threshold ORR for the UC cohort will be 20%. The sample size at this dose level for the UC cohort will be expanded to a total of 30 subjects (20 additional subjects to the 10 subjects included in the interim evaluation in the expansion part) if the probability of the ORR exceeding 20% is ≥60%. That is, if ≥2 of 10 subjects respond, the cohort will be expanded. The cohort will not be expanded if there is <60% probability that the ORR is ≥20%.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation.

Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRB. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator or subinvestigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor and the IRB for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to the IRB. In these cases, the sponsor may be required to send a letter to the head of the medical institution detailing such changes.

11.2 Adherence to the Protocol

The investigator or subinvestigator will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The head of the medical institution will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with GCP. All records at the site are subject to inspection by the local auditing agency and to IRB review.

In accordance with GCP, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs,

rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each consented subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following items that are not included in any medical records, the data recorded directly on the CRF are to be considered source data :

- Study drug compliance (eg, reason for treatment withdrawal, reason for and any change of dosage)
- Indication for prior/concomitant medication (drug/therapy)
- Discontinuation information (eg, in case of lost to follow-up due to subject choice)
- Sampling date and time for the drug concentration
- Sampling date for the clinical laboratory tests
- Comments and other information on AEs (eg, severity, relationship to study drug, outcome)
- Race, ethnicity

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator, the head of the medical institution, or the designated representative is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs and IRB correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period the medical institution contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of GCP and all applicable local regulations. The government regulatory authority may request an inspection during the study or after its completion.

11.8 Handling of Study Drug

All study drugs will be supplied to the pharmacist or its designee by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The pharmacist or its designee must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The pharmacist or its designee must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the pharmacist or its designee will return all unused drugs, and a copy of the completed drug disposition form (upon request) to the sponsor.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission.

The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each head of the medical institution and the sponsor.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the subinvestigator, the investigator's staff, and the IRB and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Clinical Trial Agreement executed between the sponsor and the head of the medical institution.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Clinical Trial Agreement executed between the head of the medical institution and the sponsor.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/the heads of the medical institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/the head of the medical institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the head of the medical institution where applicable, and the investigator/the head of the medical institution should promptly inform the sponsor and the IRB and provide the sponsor and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 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 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 determination of MTD may be made.

Appendix 2 Eastern Cooperative Oncology Group Performance Status(ECOG-PS)

Scale	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Adapted from Oken MM, et al. Am J Clin Oncol. 1982; 5: 649-55.

Appendix 3 Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1)

In principal, tumor assessment is evaluated based on RECIST 1.1 by the investigator of subinvestigator. Chest X-rays will not be used to evaluate target lesions.

Tumor Response Assessment

1. Baseline assessment

When 2 or more measurable lesions are seen in the baseline evaluation, a maximum total of 5 lesions that represent all permeated organs (no more than 2 lesions per organ) will be selected as target lesions, and measurements at baseline assessment will be recorded. The sum of the diameters (hereinafter, diameter sum: Longest diameter for tumor lesions, short axis for lymph node lesions) for all target lesions at baseline assessment will be calculated as the baseline diameter sum. Lesions (or lesion sites) other than target lesions shall be considered non-target lesions and will be recorded at baseline evaluation. It is not necessary to measure these non-target lesions, and qualitative assessment only will be performed at the time prescribed by the protocol.

2. Definition of measurable and unmeasurable

Tumor lesions and lymph nodes at baseline assessment will be classified as either "measurable" or "unmeasurable" based on the below criteria.

Definition of measurable and unmeasurable lesions

Measurable	Tumor lesions	≥10 mm by CT scan (CT scan slice thickness no greater than 5 mm) ≥10 mm caliper measurement by clinical examination
	Lymph node lesions	≥15 mm in short axis when assessed by CT
Unmeasurable	Tumor lesions	Longest diameter <10 mm
	Lymph node lesions	Lymph nodes with 10 to <15 mm short axis

3. Criteria for judging the response of target lesions

The criteria used to determine tumor response for target lesions is shown below.

Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. All lymph nodes selected as target lesions must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the diameter sum of target lesions, taking as reference the baseline diameter sum.
Progressive Disease (PD)	At least a 20% increase in the diameter sum of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest diameter sum while on study.

4. Criteria for judging the response of non-target lesions

The criteria used to determine tumor response for non-target lesions is shown below.

Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/non-PD	Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions.

5. Overall response

Overall response is judged from the combination of responses of target and non-target lesions as well as the appearance or not of new lesions at the point prescribed in the protocol. Overall response will be judged at each point of time in accordance with the following table when the baseline has target lesions.

Time Point Response: Patients with Target (+/–non-target) Disease

Target lesions	Non-target lesions	Appearance of new lesions	Overall response
CR	CR	No subjects	CR
CR	Non-CR/non-PD	No subjects	PR
CR	Not evaluated	No subjects	PR
PR	Non-PD or not all evaluated	No subjects	PR
SD	Non-PD or not all evaluated	No subjects	SD
Not all evaluated	Non-PD	No subjects	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Appendix 4 New York Heart Association (NYHA) Cardiac Disease Classification

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

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

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

Appendix 5 Common Terminology Criteria for Adverse Events(CTCAE)Version 4.03

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

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

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

ADL = activities of daily living.

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.03

For further details regarding MedDRA, refer to the MedDRA website at:
http://www.meddra.org

Appendix 6 Security, Use, and Retention of the Samples for Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research, and Subject Privacy Protection

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example analysis of protein expression, DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single coded (subject ID Number) (according to the ICH E18 draft guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used for the research of this study.

Subject Privacy and Return of Data

Samples will be single coded (subject ID Number). No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample.

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this study or research. These include:

- Medical institutions
- Clinical research organizations retained by the sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in the clinical study report (or may be presented in the separately prepared report) which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analyses, individual analyzed data are not currently anticipated to have clinical relevance to the subjects or their family members, and the timing of analysis is not decided. Therefore, these results will not be disclosed to the subjects.