

## 2. Summary

<b>Sponsor:</b> Eisai Co., Ltd.	<b>Clinical study summary</b>  Relevant section in application dossier Section No.:	(For use by reviewing authorities)
<b>Product name:</b> Undefined		
<b>Effective component:</b> Undefined (JAN)		
<b>Title of Study:</b> Phase I Clinical Study of E7080		
<b>Principle investigator:</b> Tomohide Tamura, Chief of General Inpatient Division, National Cancer Center Hospital		
<b>Medical institution:</b> National Cancer Center Hospital, Department of Respiratory Diseases		
<b>Published literature (Literature reporting results of this clinical study)</b> None		
<b>Clinical study period:</b> Approximately 2 years, 8 months January 24, 2006 (Date informed consent of first patient acquired) September 8, 2008 (Last day of tests/observations of final patient)		<b>Development phase:</b> Phase I
<b>Objectives:</b> The objective is to investigate the following through twice daily repeated oral administration of E7080 for 2 weeks, in patients with solid tumor which is resistant to approved conventional anti-tumor therapies, or for which no appropriate treatment is available. Primary objective: To estimate the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) when E7080 is repeatedly administered in 3-week cycles composed of 2 weeks of twice daily repeated administration followed by a 1-week withdrawal period. Secondary objectives: (1) Conduct an exploratory investigation of the pharmacokinetics of E7080. (2) Investigate the safety and tolerability of E7080. (3) Provide an estimate for the recommended dose in phase II clinical trials of E7080. (4) Observe the anti-tumor effect of E7080 in patients in whom this can be evaluated. (5) Conduct an exploratory analysis of the pharmacodynamic markers of E7080.		
<b>Clinical study method:</b> Single-center, open-label, sequential dose-escalation study		
<b>Sample size (planned and at time of analysis):</b> Planned sample size : 40 patients (projected) At the time of analyses : Registered subjects : 28 (3 subjects at 0.5, 1, 2, 9, 13, and 16 mg BID; 4 subjects at 4, and 6 mg BID, and 2 subjects at 20 mg BID) Treated subjects : 27 (3 subjects at 0.5, 1, 2, 4, 9, 13, and 16 mg BID; 4 subjects at 6 mg BID, and 2 subjects at 20 mg BID) Safety analysis set : 27 subjects (3 subjects at 0.5, 1, 2, 4, 9, 13, and 16 mg BID; 4 subjects at 6 mg BID, and 2 subjects at 20 mg BID) Tolerability analysis set : 26 subjects (3 subjects at 0.5, 1, 2, 4, 6, 9, 13, and 16 mg BID; and 2 subjects at 20 mg BID) Pharmacokinetics analysis set : 27 subjects (3 subjects at 0.5, 1, 2, 4, 9, 13, and 16 mg BID; 4 subjects at 6 mg BID, and 2 subjects at 20 mg BID) Pharmacodynamics analysis set : 26 subjects (3 subjects at 0.5, 1, 2, 4, 6, 9, 13, and 16 mg BID; and 2 subjects at 20 mg BID) Efficacy analysis set : 26 subjects (3 subjects at 0.5, 1, 2, 4, 6, 9, 13, and 16 mg BID; and 2 subjects at 20 mg BID)		
<b>Diagnosis and inclusion criteria:</b> <ul style="list-style-type: none"> <li>• Targetted disease Solid tumors</li> <li>• Inclusion criteria           <ol style="list-style-type: none"> <li>(1) Patients who have a histologically and/or cytologically confirmed solid tumor.</li> <li>(2) Patients with a solid tumor which was resistant to approved conventional anti-tumor therapies, or for which no appropriate treatment is available</li> <li>(3) Patients for whom all previous treatments (including surgery and radiotherapy), blood transfusions, and use of blood agents, and hematopoietic factors such as G-CSF, concluded at least 4 weeks before enrollment, and with the exception of alopecia, have no sign of Grade 2 or higher toxicity carried over from the previous treatment</li> <li>(4) Patients 20 years or older and less than 75 years of age at the time of enrollment</li> <li>(5) Patients with 0-1 of Performance Status (PS) established by Eastern Cooperative Oncology Group (ECOG)</li> </ol> </li> </ul>		

- (6) Patients who can stay remain hospitalized for more than 1 cycle for treatment
- (7) Patients expected to survive for more than 3 months from the start of study drug administration
- (8) Patients who have submitted written informed consent for the participation in the study
- Exclusion criteria
  - (1) Patients with brain metastasis who have clinical symptoms or require treatment
  - (2) Patients with any of the following laboratory values at the time of screening:
    - 1) Hemoglobin <9.0 g/dL
    - 2) Neutrophil count <1.5×10<sup>3</sup>/μL
    - 3) Platelet count <10×10<sup>4</sup>/μL
    - 4) Serum bilirubin >1.5 mg/dL
    - 5) AST >100 IU/L
    - 6) ALT >100 IU/L
    - 7) Serum creatinine >1.5 mg/dL  
or creatinine clearance measured by the Cockcroft-Gault method <50 mL/min  
(Creatinine clearance is calculated using the following formula:  
Men : (140 – Age) × Body weight ÷ (Serum creatinine × 72)  
Women : 0.85 × (140 – Age) × Body weight ÷ (Serum creatinine × 72))
  - (3) Patients with positive reaction for HIV or HCV antibody or HBs antigen or with severe infection that requires treatment
  - (4) Patients who have a history of ischemic heart disease including myocardial infarction or clinically significant cardiac disorders within 6 months before registration of this study
  - (5) Patients with the following prolongation of QT/QTc interval at screening: Men: QTc >450 msec; Women: QTc >470 msec (Fridericia method) Or patients with arrhythmia (atrial fibrillation, etc.) that requires treatment
  - (6) Patients who have a history of cerebral infarction or have hemorrhagic or thrombotic disease Patients using antiplatelet/anticoagulant drugs including aspirin, warfarin, and ticlopidine at screening and must use it during this clinical study
  - (7) Patients whose mean systolic blood pressure is 160 mmHg or higher and diastolic blood pressure is 90 mmHg or higher at resting, when measured 2 or more times during screening
  - (8) Patients with proteinuria measured at 2+ or higher in qualitative test for urinary protein at screening
  - (9) Patients presenting (or with a history of) malabsorption syndrome or patients who have undergone surgery involving gastrointestinal anastomoses within 4 weeks prior to enrollment in this study or patients who have undergone surgery within 3 weeks prior to enrollment and have yet to recover
  - (10) Patients with a mental or physical disease such as alcoholism or drug addiction who are judged by the principal investigator or other investigator to be unable to comply with the study protocol
  - (11) Patients who received any other investigational drug within 4 weeks prior to enrollment in this study
  - (12) Patients using itraconazole, erythromycin, clarithromycin, diltiazem, or verapamil (drugs that inhibit the metabolizing enzyme CYP3A4) at the time of screening and who must continue to use these drugs during this study
  - (13) Pregnant or nursing women (All female patients with the potential to become pregnant must be confirmed to be not pregnant prior to enrollment. Postmenopausal women must be amenorrheic for at least 12 months. Female patients must use appropriate contraception.)
  - (14) Fertile male patients who refuse to use contraception.
  - (15) Patients judged to be ineligible to participate in this study by the principal investigator or other investigator

#### **Dosage and administration of study drug/control drug and batch numbers**

Study drug: E7080 Control drug: None

Dosage and administration:

Doses: 1, 2, 4, 8, 12, 18, 26, 32, and 40 mg/day

Administration method: In Cycle 0, half the dose in each dose group (single dose that is administered twice daily) was administered one time on the morning of day 1. From Cycle 1 on, the relevant dose was halved and orally administered twice daily at 12-hour intervals in the morning and evening. However, on day 14 of Cycle 1, the drug was administered in the morning only in order to evaluate pharmacokinetics. The duration of 1 cycle was 3 weeks during which E7080 was repeatedly administered for 2 weeks, followed by a 1-week withdrawal period. Treatment could continue at the same dose from Cycle 2 on, unless the subject met the criteria for discontinuation of the study. From Cycle 2 on, treatment was administered twice daily on all treatment days.

Dose escalation plan: While monitoring safety, the dose was to be escalated in 3 to 6 subjects at each dose. First, 3 subjects were enrolled in each dose group. In consideration of the subjects' safety, the first subject in each dose group was monitored from the start of treatment for at least 2 days, before treatment in the second and subsequent subjects was initiated (beginning no early than day 3 of treatment of the first subject). If DLT did not occur in any of the 3 subjects between the start of treatment in Cycle 0 and 3 weeks after the start of treatment in Cycle 1, treatment was shifted to the next dose level beginning with the next subject. If DLT occurred in 1 of 3 subjects, 3 additional subjects were added to the same dose level and investigations were continued. If DLT occurred in 2 of 3 subjects, treatment did not proceed to the next dose level. If DLT occurred in 1 of the subjects added, no more subjects were added from that time on. If DLT was not observed in any of the 3 added subjects, in other words, if DLT occurred in 1 of 6 subjects, treatment proceeded to the next dose level. If DLT occurred in 2 or more subjects at any dose level, treatment did not proceed to the next dose level. From the first dose level on, the dose was escalated 100% if toxicity occurring in subjects was Grade 1 or below. When Grade 2 toxicity occurred in 1 or more subject, the dose was subsequently escalated  $\leq 50\%$ , and if Grade 3 toxicity occurred, thereafter the dose was escalated  $\leq 33.3\%$ . All 3 subjects at each dose level were followed up for 3 weeks after the start of cycle 1 before determining the dose escalation to the next dose. Dose escalation was not performed in the same subjects.

Batch Nos.:	E7080 0.1 mg tablet	:	P53007ZZA
	E7080 1 mg tablet	:	P53012ZZA, P5X025ZZD
	E7080 10 mg tablet	:	P66011ZZC

#### Treatment period:

For Cycle 0, a single dose of E7080 was administered. Three-week cycles were established for Cycle 1 and subsequent cycles, during which E7080 was repeatedly administered (2 weeks of repeated administration of E7080 followed by a 1-week withdrawal period), and treatment could be continued provided the discontinuation criteria were not met.

#### Assessment criteria:

Efficacy : Best Overall Response based on Response Evaluation Criteria in Solid Tumor (RECIST) rules, tumor markers

Safety : Adverse events/adverse drug reactions, vital signs, physical findings, laboratory test values

Tolerability : DLT (primary endpoint)

Pharmacokinetics : Plasma drug concentration, serum plasma protein binding rate, urinary drug concentration

Pharmacodynamic effect : Plasma angiogenic marker concentration, circulating endothelial cells

#### Statistical procedures:

Analysis was performed using statistical analysis software SAS for Windows (release 6.12 or higher), SAS Drug Development (Ver. 3.0), WinNonlin (Professional version 4.1 or higher, Microsoft Excel and NONMEM (Version V, level 1.1 or higher). A two-sided significance level of 5% and a two-sided 95% confidence interval were used. Unless otherwise specified, multiplicity-adjusted p-values for inferences were not performed.

(1) Analysis of subject background characteristics

In the treated subjects and safety analysis set, summary statistics were calculated for continuous data by initial dose level as well as for total subject background factors. Frequency and distribution ratios (%) were calculated for categorical data.

(2) Analysis of efficacy

In the efficacy analysis set, the numbers of subjects showing Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE) were calculated by initial dose level, and also tabulated for total evaluable subjects to determine the best overall response (Best Overall Response based on Response Evaluation Criteria in Solid Tumor [RECIST] rules). In the case of parameters that are tracked over time such as tumor markers, the data was graphed by subject.

(3) Analysis of safety

In the safety analysis set, the numbers of subjects experiencing adverse events and adverse drug reactions were tabulated by symptom/finding (SOC/PT) and NCI-CTC Grade by initial dose level and total. The times of occurrence of adverse events that were regarded as significant were also tabulated. In addition, graphs or tables showing changes over time were prepared for each laboratory test parameter, vital sign, and other physical findings observed over time.

(4) Analysis of tolerability

In the tolerability analysis set, DLT occurrences were tabulated by initial dose level as well as total.

(5) Analysis of pharmacokinetics

PK analyses will be based on the Pharmacokinetic Analysis Set. PK profile of E7080 was evaluated by preparing concentration-time charts. Pharmacokinetic parameters, including those listed below, were calculated from plasma E7080 concentrations using model independent analysis. Renal clearance was calculated from plasma and urinary E7080 concentrations. In addition, dose proportionality was investigated using  $C_{max}$  and AUC obtained by model independent analyses. Serum protein binding rates were calculated based on serum E7080 concentrations and unbound E7080 concentrations.

The relationship of pharmacokinetics with pharmacodynamics, safety, and efficacy were also analyzed.

## &lt;Pharmacokinetic parameters&gt;

Maximum observed plasma concentration ( $C_{max}$ ), time at which the highest drug concentration ( $t_{max}$ ), area under the plasma concentration-time curve (AUC), terminal phase rate constant ( $\lambda_z$ ), terminal phase half life ( $t_{1/2}$ ), apparent volume of distribution at terminal phase ( $V_z/F$ ), mean residence time (MRT), apparent clearance following oral administration ( $CL/F$ ), and renal clearance ( $CL_R$ )

## (6) Analysis of pharmacodynamic markers

In the pharmacodynamics analysis set, changes in plasma angiogenic marker levels and circulating endothelial cells before and after E7080 treatment were analyzed. The relationship between efficacy or safety and changes in plasma protein concentrations and circulating endothelial cells was also investigated.

**Summary—Conclusion**Tolerability results

In groups administered 0.5, 1, 2, 4, 6, 9, or 13 mg BID (3 subjects per group) there were no adverse events equivalent to DLT in Cycles 0 or 1, and tolerability investigations continued while escalating the dose up to 20 mg BID. Grade 3 platelet count decreased was seen in 2 of 2 subjects in the 20 mg BID group. As a result, 20 mg BID was judged to be an “intolerable dose”, 3 subjects were added at 16 mg BID, an intermediate dose between 13 and 20 mg BID, and the tolerability was investigated. The results showed that DLT occurred in 1 of 3 subjects in the 16 mg BID group (Grade 3 aspartate aminotransferase increased and alanine aminotransferase increased). In addition, in the other 2 subjects in the 16 mg BID group, Grade 2 platelet count decreased and fatigue were observed in Cycle 2 in one subject, while in the other subject, Grade 3 fatigue and protein urine present were observed in Cycle 2 as well as Grade 2 oedema, and analyses of 16 mg BID was concluded without adding a third subject. Results of investigations by the Efficacy and Safety Committee also revealed DLT occurring in 1 of 3 subjects at 16 mg BID, and toxicity equivalent to DLT was also observed in the other 2 subjects in Cycle 2 and thereafter. Consequently, MTD was judged to be 13 mg BID, and the recommended dose was estimated at 13 mg BID.

Results of pharmacokinetics analyses

In Cycle 0, pharmacokinetics were investigated following administration of a single dose of 0.5 to 20 mg of E7080 in 27 subjects with solid tumor (3 subjects each at 0.5, 1, 2, 4, 9, 13, and 16 mg BID, 4 subjects at 6 mg BID, and 2 subjects at 20 mg BID). After administering the single dose in Cycle 0, and a 7- to 9-day withdrawal period had elapsed, Cycle 1 was initiated during which 0.5 to 20 mg of E7080 was orally administered to the same subjects twice daily in the morning and evening, for 14 days (twice daily for 13 days, administered in morning only of day 14) and the pharmacokinetics were investigated. An adverse event (postrenal failure) occurred in Subject No. PPD [REDACTED] (6 mg BID group) on day 2 of Cycle 0, and as a result treatment was discontinued on day 4 of that same cycle. In addition, treatment was not administered to Subject PPD [REDACTED] (20 mg BID group) in the evening of day 13 and the morning of day 14 of Cycle 1. As a result, pharmacokinetics analyses following repeated administration of E7080 did not include these 2 subjects, but was analyzed in the 25 other subjects (3 subjects each at 0.5, 1, 2, 4, 6, 9, 13, and 16 mg BID, and 1 subject at 20 mg BID). Summary statistics for the groups administered 0.5 to 16 mg BID (excluding the 20 mg BID group which had fewer than 3 subjects receiving treatment) were used in analyses of the pharmacokinetic parameters described below. In addition, E7080 was administered under fasting conditions when first administered and in the morning of day 14 of Cycle 1, otherwise it was administered at least 1 hour after eating.

The concentration of E7080 in the plasma after administration of a single dose reached  $C_{max}$  at a median time of 1 to 5 hours, and then decreased first rapidly then gradually, with a mean  $t_{1/2}$  of 19.1 to 46.5 hours. Mean  $CL/F$  was 4.5 to 7.2 L/hr and the mean  $V_z/F$  was 136 to 312 L.

At each dose, the mean plasma concentrations before administration in the morning of day 5, 8, and 11 during twice daily administration of E7080 were about the same.

The concentration of E7080 in the plasma when repeatedly administered for 14 days displayed similar changes over time to those following single-dose administration, reaching  $C_{ss,max}$  at a median of 1 to 3 hours, followed by elimination at a rate of  $t_{1/2,ss}$  of 25.6-37.1 hours (mean values). In addition,  $CL_{ss}/F$  was 3.5 to 5.6 L/hr, and  $V_{ss}/F$  was 155 to 261 L. Ratios between pharmacokinetic parameters on day 14 to day 1 were calculated. Theoretical values based on  $t_{1/2}$  after single-dose administration ( $R_{ac}$ ) ranged from 2.8 to 6.1, while  $R_{ac}$  ( $C_{max}$ ) resulting from a comparison of  $C_{max}$  levels was between 1.5 and 6.9, and  $R_{ac}$  (AUC) produced by comparing  $AUC_{0-12}$  levels was between 1.6 and 5.6, as values were similar to theoretical values.  $R_{ss}$ , the ratio of  $AUC_{0-\tau}$  values after repeat-dose administration to  $AUC_{0-inf}$  after single-dose administration was between 1.1 and 1.4.

In Cycle 1, urine was collected for 12 hours after administration in the morning of day 14 of repeat-dose treatment (a time equivalent to the interval between doses) and the urinary excretion of E7080 was investigated. Urinary excretion  $fe_{0-\tau}$  was 0.5 to 2.0%, and  $CL_R$  was 17.4 to 84.6 mL/hr (0.0174 L/hr to 0.0846 L/hr), with no uniform trends of higher values occurring at higher doses.

A visual examination of dose proportionality based on pharmacokinetic parameters obtained through model independent analyses ( $C_{max}$ ,  $AUC_{0-inf}$ ,  $C_{ss,max}$  and  $AUC_{0-\tau}$ ) showed increases that corresponded to the dose in all parameters except  $C_{max}$ . In addition, in the equation  $Y = \alpha X^\beta$  with the dose as X and pharmacokinetic parameters as Y, point estimates for  $\beta$  and 95% confidence intervals were as follows:  $C_{max}$ : 1.52 [1.42–1.63];  $AUC_{0-inf}$ : 1.01 [0.92–1.10];  $C_{ss,max}$ : 1.09 [0.97–1.21]; and  $AUC_{0-\tau}$ : 1.01 [0.90–1.12]. Except for  $C_{max}$ , point estimates for  $\beta$  were values near 1, and the 95% confidence interval for  $\beta$  was within the standard range for dose proportionality (0.7 to 1.3).

E7080 concentration in the serum and unbound E7080 concentration were measured 3 hours after administration in the morning of day 14 of repeat-dose administration, and the serum protein binding rates were calculated. The results showed serum protein binding of E7080 of 96.6 to 98.2%, and no major variations in serum protein binding were seen in the concentration range of 26 ng/mL to 574 ng/mL obtained in this study.

Safety results:

Adverse event incidence rates in the safety analysis set were 100% in each initial dose level (3/3 subjects at 0.5, 1, 2, and 4 mg BID; 4/4 subjects at 6 mg BID, 3/3 subjects at 9, 13, and 16 mg BID, and 2/2 subjects at 20 mg BID). Incidences for adverse drug reactions (adverse events for which a causal relationship with the investigational drug cannot be overruled) were also 100% in each initial dose level (3/3 subjects at 0.5, 1, 2, and 4 mg BID; 4/4 subjects at 6 mg BID, 3/3 subjects at 9, 13, and 16 mg BID, and 2/2 subjects at 20 mg BID).

Adverse events occurring at an incidence rate of  $\geq 50\%$  in total initial dose level were: blood urine present (74.1%, 20/27 subjects); fatigue (70.4% 19/27 subjects); hypertension (66.7%, 18/27 subjects); headache (63.0%, 17/27 subjects), aspartate aminotransferase increased (63.0%, 17/27 subjects); protein urine present (63.0%, 17/27 subjects); diarrhoea (55.6%, 15/27 subjects); alanine aminotransferase increased (55.6%, 15/27 subjects), and blood lactate dehydrogenase increased (51.9%, 14/27 subjects). Adverse drug reactions that occurred at an incidence rate of  $\geq 50\%$  were: fatigue (66.7%, 18/27 subjects), blood urine present (66.7%, 18/27 subjects), headache (63.0%, 17/27 subjects), protein urine present (63.0%, 17/27 subjects), diarrhoea (51.9%, 14/27 subjects); and aspartate aminotransferase increased (51.9%, 14/27 subjects).

Nine serious adverse events including death were observed in 7 subjects (1 event in 1 subject at 0.5 mg BID; 3 events in 3 subjects at 6 mg BID; 4 events in 2 subjects at 9 mg BID; and 1 event in 1 subject at 20 mg BID). Included among these was 1 death in the 9 mg BID group (Subject No. PPD [REDACTED] cause of death: worsening of underlying disease).

Forty-five significant adverse events (adverse events that resulted in discontinuation of the investigational drug treatment or adverse events judged to be Grade 3 or 4 severity) were observed in 18 subjects: 2 events in 1 subject at 0.5 mg BID; 3 events in 2 subjects at 2 mg BID; 2 events in 1 subject at 4 mg BID; 5 events in 3 subjects at 6 mg BID; 10 events in 3 subjects at 9 mg BID; 9 events in 3 subjects at 13 mg BID, 6 events in 3 subjects at 16 mg BID, and 8 events in 2 subjects at 20 mg BID. These included the following adverse drug reactions that occurred in 2 or more subjects: hypertension (5 cases in 5 subjects); platelet count decreased (4 cases in 3 subjects); and diarrhoea, protein urine present, aspartate aminotransferase increased, and alanine aminotransferase increased (2 cases in 2 subjects each).

Efficacy results:

The tumor reduction effect was evaluated based on RECIST criteria in the 25 subjects in the efficacy analysis set who could be evaluated for tumor reduction effect by RECIST (evaluable subjects).

PR was observed in 1 subject at 2 mg BID (Subject No.: PPD [REDACTED]). This subject was a patient with colon cancer (with mediastinal lymph node and lung metastases) in which PR was observed in Cycles 4, 6, and 8, but PD occurred in Cycle 10 and the study was discontinued. Treatment could be continued for 6 or more cycles in 10 of 27 subjects. These consisted of 2 subjects at the 0.5 mg BID groups (corpus uteri cancer: 6 cycles; colon cancer: 12 cycles); 1 subject at 1 mg BID (non-small cell lung cancer: 6 cycles); 2 subjects at 2 mg BID (colon cancer: 10 cycles; colorectal cancer: 6 subjects); 1 subject at 4 mg BID (colon cancer: 10 cycles); 1 subject at 6 mg BID (small intestine cancer: 10 cycles); 1 subject at 9 mg BID (non-small cell lung cancer: 10 cycles); 1 subject at 13 mg BID (peritoneal cancer: 8 cycles); and 1 subject at 16 mg BID (breast cancer: 12 cycles).

Pharmacodynamic effect results

The plasma angiogenic markers that increased after administration of E7080 were VEGF (increased  $\geq 300\%$  at doses of  $\geq 6$  mg BID); SDF1 $\alpha$  (increased about 100% at doses of  $\geq 9$  mg BID); and thrombopoietin (increased at doses of  $\geq 13$  mg BID). On the other hand, the plasma angiogenic markers of sVEGFR1 decreased, and sVEGFR2 showed a tendency to decrease. There were subjects with increased HGF and SCF at high dose levels, but no clear dose-dependent changes were observed. PDGF-BB showed virtually no change, but abruptly decreased at high toxic dose levels.

The results of investigations of variations in circulating endothelial cells showed that CEP decreased as a result of E7080 administration. However, only c-Kit-positive CEP decreased, as there was no change in c-Kit-negative CEP. CEC decreased in some subjects as a result of E7080 administration and decreased in others, but in most subjects c-Kit-positive CEC decreased and c-Kit-negative CEC increased.

VEGF, SCF, SDF1 $\alpha$ , and thrombopoietin are involved in driving CEP to angiogenesis sites, and are important in angiogenesis that can be observed by variations in CEC. These factors were analyzed together with changes in CEC and CEP, but no significant correlation was observed. However, results of investigation of data based on the presence or absence of c-Kit (CD117) revealed a significant negative correlation (Spearman's rank correlation coefficient:  $-0.457$ ,  $-0.466$ ; p-value: 0.021, 0.018) as the decrease in the percentage of CEP: c-Kit-positive results was larger in patients the higher their SCF and SDF1 $\alpha$  levels. On the other hand, there was no significant correlation to the percentage of CEC: c-Kit-positive results. There was also a positive correlation between thrombopoietin and c-Kit-negative CEC (Spearman's rank correlation coefficient: 0.520; p-value: 0.011).

In all 25 subjects used in these analyses there was no significant correlation between variations in the percentage of CEC: c-Kit-positive findings and the percentage of CEP: c-Kit positive results, however, analyses of the results in the 20 subjects in dose groups administered the MTD or below (13 mg BID) showed a significant positive correlation between variations in the percentage of CEC: c-Kit positive results and the percentage of CEP: c-Kit positive results (Spearman's rank correlation coefficient: 0.496; p-value: 0.026). At doses at or below MTD (13 mg BID) which will actually be used in E7080 therapy, there was a correlation in the variations in CEC and CEP when there was a high level c-Kit expression.

#### Relationship between pharmacokinetics and pharmacodynamic markers, safety or efficacy

Pharmacokinetic parameters resulting from repeated administration obtained by model independent analysis ( $C_{ss,max}$ ,  $C_{ss,min}$ , and  $AUC_{0-\tau}$ ) were plotted against pharmacodynamic markers (plasma angiogenic markers and variations in circulating endothelial cells), safety results (laboratory test values showing changes [platelet count, AST, and ALT] and adverse event Grade) and efficacy data (treatment duration and therapeutic effect [classified by best overall response and SD duration]) for all subjects in exploratory investigations.

SDF1 $\alpha$  tended to increase as  $C_{ss,max}$ ,  $C_{ss,min}$  and  $AUC_{0-\tau}$  increased (Spearman's rank correlation coefficients were 0.754, 0.772, and 0.774, with p-values of <0.001, <0.001, and <0.001 for  $C_{ss,max}$ ,  $C_{ss,min}$  and  $AUC_{0-\tau}$ , respectively. sVEGFR2 tended to decrease as  $C_{ss,max}$ ,  $C_{ss,min}$  as  $AUC_{0-\tau}$  increased (Spearman's rank correlation coefficients were -0.925, -0.942, and -0.931, with p-values of <0.001, <0.001, and <0.001 for  $C_{ss,max}$ ,  $C_{ss,min}$  and  $AUC_{0-\tau}$ , respectively. No significant correlations between variations in circulating endothelial cells and pharmacokinetic parameters were observed. Platelet counts tended to decrease as  $C_{ss,max}$ ,  $C_{ss,min}$  and  $AUC_{0-\tau}$  increased (Spearman's rank correlation coefficients were -0.637, -0.652, and -0.636, with p-values of <0.001, <0.001, and <0.001 for  $C_{ss,max}$ ,  $C_{ss,min}$  and  $AUC_{0-\tau}$ , respectively. Significant correlations between percent increase of AST and ALT and pharmacokinetic parameters were observed. (Spearman's rank correlation coefficients of 0.509, 0.551, and 0.497 with p-values of 0.009, 0.004, and 0.012 for AST:  $C_{ss,max}$ ,  $C_{ss,min}$ , and  $AUC_{0-\tau}$ , respectively; and Spearman's rank correlation coefficients of 0.429, 0.463, and 0.408, with p-values of 0.032, 0.020, and 0.043 for ALT:  $C_{ss,max}$ ,  $C_{ss,min}$ , and  $AUC_{0-\tau}$ , respectively). The following adverse events showed significant correlation with  $C_{ss,max}$ ,  $C_{ss,min}$ , and  $AUC_{0-\tau}$ : urinary protein positive: Spearman's rank correlation coefficients of 0.518, 0.599, and 0.558 with p-values of 0.008, 0.002, and 0.004 for  $C_{ss,max}$ ,  $C_{ss,min}$ , and  $AUC_{0-\tau}$ , respectively; hypertension: Spearman's rank correlation coefficients of 0.527, 0.538, and 0.543 with p-values of 0.007, 0.006, and 0.005 for  $C_{ss,max}$ ,  $C_{ss,min}$ , and  $AUC_{0-\tau}$ , respectively; and fatigue: Spearman's rank correlation coefficients of 0.509, 0.447, and 0.471 with p-values of 0.009, 0.025, and 0.017 for  $C_{ss,max}$ ,  $C_{ss,min}$ , and  $AUC_{0-\tau}$ , respectively. In addition, there were significant correlations between decreased platelet counts and  $C_{ss,max}$  and  $AUC_{0-\tau}$  (Spearman's rank correlation coefficients of 0.419, 0.355, and 0.398 with p-values of 0.037, 0.082, and 0.049 for  $C_{ss,max}$ ,  $C_{ss,min}$ , and  $AUC_{0-\tau}$ , respectively). There was no significant correlation between adverse event severity and pharmacokinetic parameters. There was no significant correlation between duration of treatment and pharmacokinetic parameters. And there was no significant correlation between therapeutic effect (classification by best overall response and SD duration).

#### Relationship between pharmacodynamic markers and safety or efficacy

Changes in pharmacodynamic markers were plotted against safety data (adverse event Grade and percent change in laboratory test value) and efficacy data (treatment duration and therapeutic effect [classified by best overall response and SD duration]) for all subjects in exploratory investigations.

Significant correlations were seen between the grade of hypertension and VEGF, sVEGFR1, and sVEGFR2 (Spearman's rank correlation coefficients of 0.452, -0.527, and -0.594, with p-values of: 0.045, 0.005, and 0.001) as well as with HGF, SCF, and thrombopoietin (Spearman's rank correlation coefficients of 0.544, 0.449, and 0.522, with p-values of 0.004, 0.021, and 0.007). Significant correlations were observed between urinary protein positive data and VEGF, sVEGFR1, and sVEGFR2 (Spearman's rank correlation coefficients of 0.535, -0.481, and -0.638, with p-values of 0.015, 0.012, and <0.001,) as well as for HGF and SDF1 $\alpha$  (Spearman's rank correlation coefficients of 0.518, and 0.398, with p-values of 0.006 and 0.044). Significant correlations were seen in the Grade of platelet count decrease with sVEGFR1 and sVEGFR2 (Spearman's rank correlation coefficients: -0.609 and -0.501 with p-values of 0.001 and 0.009), as well as with SCF and thrombopoietin (Spearman's rank correlation coefficients: 0.523 and 0.459 with p-values of 0.006 and 0.020). There were no pharmacodynamic markers showing a significant correlation with the grade of AST or ALT increase, which are attributable to hepatic dysfunction. There was also a significant correlation between grade of increase of gamma-glutamyltransferase and SCF (Spearman's rank correlation coefficient: 0.530, p-value: 0.005). There were significant correlations between grade of fatigue and VEGF, sVEGFR2 and HGF (Spearman's rank correlation coefficients of 0.510, -0.408, and 0.460, with p-values of 0.021, 0.038 and 0.017). There were no pharmacodynamic markers showing a correlation with grade of diarrhoea. There was also a significant correlation between percent decrease in platelet counts and decrease in the percentage of CD117-positive CEP positive rate (Spearman's rank correlation coefficient: -0.418, p-value: 0.037), suggesting the possibility of a shared mechanism within the hematopoietic system.

There were significant correlations between the percent change in platelet count and VEGF, SDF1 $\alpha$ , sVEGFR1, sVEGFR2 and thrombopoietin (Spearman's rank correlation coefficients of -0.568, -0.626, 0.464, 0.786 and -0.477, with p-values of 0.009, <0.001, 0.016, <0.001 and 0.016). There was also a significant correlation between percent change in platelet count and percentage of CD117-positive CEP (Spearman's rank correlation coefficient: 0.416, with a p-value of 0.038).

There was a significant correlation between percent change in AST and sVEGFR1 (Spearman's rank correlation coefficient: -0.600, p-value: 0.001). There was also a significant negative correlation between percent change in AST and percentage of CD117-positive CEP (Spearman's rank correlation coefficient: -0.475; p-value: 0.016).

There was a significant negative correlation between percent change in ALT and PDGF-BB and sVEGFR2 (Spearman's rank correlation coefficients of -0.489 and -0.526, with p-values of 0.028 and 0.005).

There were no plasma angiogenic markers showing a significant correlation to therapeutic effect in changes in pharmacodynamic markers before and after administration of E7080 in Cycle 1. However, there was a significant correlation between the decrease in c-Kit-positive CEC and therapeutic effect (Spearman's rank correlation coefficient: 0.420; p-value: 0.040). There were no significant correlations between changes in CEP or c-Kit-positive CEP and therapeutic effect. When the correlation between efficacy and baseline pharmacodynamic markers was investigated, in subjects with a high baseline SDF1 $\alpha$  level as well as subjects with high rates for CEP-c-Kit positive results, E7080 treatment duration was short, and negative correlations were observed (Spearman's rank correlation coefficients of -0.402 and -0.403, with p-values of 0.041 and 0.045). On the other hand, there was no significant correlation with the classification of the therapeutic effect.

Conclusion:

E7080 was administered orally in twice daily doses of 0.5, 1, 2, 4, 6, 9, 13, 16, or 20 mg, (in 3-week cycles composed of 2 weeks of repeated administration followed by a 1-week withdrawal period), in patients with solid tumor which was resistant to approved conventional anti-tumor therapies, or for which no appropriate treatment was available.

DLT occurred in 2 of 2 subjects at 20 mg BID, and in 1 of 3 subjects at an intermediate dose of 16 mg BID, while toxicity equivalent to DLT was observed in the other 2 subjects in Cycle 2 or later. As a result, MTD was judged to be 13 mg BID, and the recommended dose was estimated at 13 mg BID.

In evaluations of the antitumor effect (RECIST) PR was seen in 1 subject at 2 mg BID, and treatment could be continued for at least 6 cycles in 10 of the 27 subjects: 2 subjects in the 0.5 mg BID group, 1 subject at 1 mg BID; 2 subjects at 2 mg BID; 1 subject at 4 mg BID; 1 subject at 6 mg BID; 1 subject at 9 mg BID; 1 subject at 13 mg BID; and 1 subject at 16 mg BID.

Based on the above it was concluded that further investigation of the antitumor effect should be conducted while taking the occurrence of hypertension and decreased platelet counts, etc., into consideration.

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