

2 STUDY SYNOPSIS

Name of Company: Eisai Co., Ltd.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Lenvatinib hard capsules	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Lenvatinib (E7080)		
	Volume:	Page:

<p>Study Title</p> <p>A Phase 1 Study of E7080 (lenvatinib) in Subjects with Solid Tumors</p>
<p>Investigator(s)/ Site(s)</p> <p>Tomohide Tamura, MD A single site in Japan participated in the study; National Cancer Center Hospital, Tokyo.</p>
<p>Publication (Reference)</p> <p>None</p>
<p>Study Period</p> <p>15 Feb 2011 to 21 Dec 2012</p>
<p>Phase of Development</p> <p>Phase 1</p>
<p>Objective(s)</p> <p>Primary objective: To investigate the tolerability and safety of lenvatinib up to 24 mg when administered orally on a once daily dose schedule in cycles (4 weeks as 1 cycle) in subjects with solid tumors.</p> <p>Secondary objectives: To assess the pharmacokinetic (PK) profiles of lenvatinib</p> <p>Exploratory objectives To preliminarily assess the antitumor response of lenvatinib</p> <p>To explore the pharmacodynamics (PD) biomarkers of lenvatinib</p>

Methodology

This study was designed as an open-label, nonrandomized, dose-escalation Phase 1 study to investigate the tolerability and safety of lenvatinib up to 24 mg when administered once daily by continuous oral administration on a 28-day cycle in subjects with solid tumor who were resistant to standard therapies, or had no appropriate treatment available. This was a single-center clinical study.

Number of Subjects (Planned and Enrolled)

Planned: 9 to 18 subjects

Enrolled: 9 subjects

Treated: 9 subjects (3 subjects in the 20-mg QD group and 6 subjects in the 24-mg QD group)

Diagnosis and Main Criteria for Inclusion

1. Subjects with a histological and/or cytological diagnosis of solid tumor
2. Subjects with solid tumor which was resistant to standard antitumor therapies, or for which no appropriate treatment was available
3. Subjects whose toxicity of previous treatment had recovered to Grade 1 or lower (except for alopecia)
4. Subjects who had completed previous antitumor therapy (such as surgery, radiotherapy) before at least 4 weeks
5. Subjects who were 20 years or older at the time of obtaining informed consent
6. Subjects with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1
7. Subjects agreed to be hospitalized during the DLT observation period
8. Subjects who met all of the following criteria:
 - Hemoglobin ≥ 9.0 g/dL
 - Neutrophil count $\geq 1.5 \times 10^3/\mu\text{L}$
 - Platelet count $\geq 10 \times 10^4/\mu\text{L}$
 - Total bilirubin ≤ 1.8 mg/dL
 - AST ≤ 100 IU/L
 - ALT ≤ 100 IU/L
 - Serum creatinine ≤ 1.5 mg/dL or Creatinine clearance ≥ 50 mL/min
Creatinine clearance was calculated based on Cockcroft-Gault method using the following formula.
 - Male : $(140 - \text{age}) \times \text{weight} \div (\text{serum creatinine} \times 72)$
 - Female : $0.85 \times (140 - \text{age}) \times \text{weight} \div (\text{serum creatinine} \times 72)$
9. Subjects expected to survive for 12 weeks or longer
10. Males and females of childbearing potential who agreed to use appropriate contraception from the giving of consent to 30 days after study drug administration
Female subjects of childbearing potential who tested negative for pregnancy at screening
11. Subjects who voluntarily agreed to participate in this study in writing

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

E7080 capsules containing 4 mg or 10 mg of lenvatinib in free form

Initial dose and method of administration:

The dose group of lenvatinib was 20 mg QD or 24 mg QD. Initially, 3 to 9 subjects were enrolled at the 20-mg dose group, and if 20 mg was confirmed to be tolerable, 3 to 9 subjects were planned to be enrolled at the 24-mg dose group.

Lenvatinib was to be administered orally, once daily in the morning. In addition, for PK assessment, on Days 1 and 15 of Cycle 1, lenvatinib was to be administered orally in the morning after fasting the previous night (from at least 12:00 midnight), and for 2 hours after administration. However, water intake was permitted.

Dosing schedule:

Cycle 1

DLT monitoring period was from the start of administration to the morning of Day 29 in Cycle 1. If a DLT was observed, Cycle 1 should be stopped for this subject.

Cycle 2 or later

Subjects were eligible to enter Cycle 2, if they had already re-consented for the continuation of this study before study drug administration of Day 1 in Cycle 2. Subjects with a DLT in Cycle 1 were eligible to enter Cycle 2 by starting at the reduced dose after the recovery from the DLT if disease progression was not observed and written informed consent to the continuation of this study was obtained. Study drug administration in subsequent cycles was continued as long as subjects did not meet the criteria for discontinuation. Each cycle consisted of 28 days.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Not applicable.

Duration of Treatment

The study drug administration was continued unless the subject meets the criteria for discontinuation.

Assessments**Efficacy**

Tumor Response

Tumor assessments were performed by the site investigator using RECIST 1.1 (with the modification that chest x-rays was not be used for assessment of target lesions). Tumor assessments were performed at screening and every 8 weeks after the study drug administration or as clinically indicated.

Tumor response was assessed using the following 3 parameters:

- Best overall response
- Objective response rate (ORR): Defined as complete response (CR) + partial response (PR).
- Disease control rate (DCR): Defined as CR + PR + stable disease (SD). SD should be ≥ 7 weeks after the first dose of study drug.

Pharmacokinetics

Plasma concentrations of lenvatinib were analyzed, and PK profiles of lenvatinib were evaluated.

Pharmacodynamics

The PD markers below were measured from blood samples.

- Angiogenesis markers in plasma (FGF-2, G-CSF, HGF, IL-10, IL-6, IL-8, PDGF-BB, SCF, SDF-1 alpha, VEGF)
- Circulating endothelial cells (CD45⁺, CD117⁺/CD133⁺, CD117⁺/CD133⁻, CD117⁻/CD133⁺, CD117⁻/CD133⁻)

Pharmacogenomics/Pharmacogenetics

Not applicable.

Safety

The following safety assessments were performed: Adverse events (AEs) (evaluated by determining the AE grade according to Common Terminology Criteria for Adverse Events [CTCAE] version 4.0), laboratory tests, vital signs (blood pressure [mm Hg], heart rate [beats per minute], body temperature [°C], and body weight [kg]), 12-lead electrocardiograms (ECGs; heart rate [bpm], QT [msec] and QTc [msec]) and ECOG-PS.

Bioanalytical Methods

Plasma concentration of lenvatinib was determined using a specific and selective method that had been suitably validated using liquid chromatography/mass spectrometry/mass spectrometry (LS/MS/MS).

Statistical Methods**Safety Analysis Set:**

The Safety Analysis Set consisted of subjects who had received at least 1 dose of study drug and had at least 1 postdose safety assessment.

Pharmacokinetic Analysis Set:

The PK Analysis Set consisted of subjects who had sufficient pharmacokinetic data to derive at least 1 PK parameter.

Efficacy

All efficacy analyses were conducted based on the Safety Analysis Set.

Best overall response was summarized by dose group and overall. Objective response rate (ORR) and disease control rate (DCR) were provided with corresponding exact 95% confidence interval (CI) by dose group and overall. Graphical displays of percent shrinkage of summed diameters in target lesion over time were provided for each patient. In addition, percent shrinkage of tumor summed diameter from baseline to the nadir was graphically presented (waterfall plot). Graphical displays of tumor markers over time were also provided for each patient.

Pharmacokinetics:

The PK Analysis Set was used for all other analyses such as the summaries of plasma concentrations and PK parameters of lenvatinib. PK profile of lenvatinib was evaluated by preparing concentration-time charts. Using non-compartmental analysis, plasma concentrations of lenvatinib was analyzed to determine the PK parameters including C_{\max} , t_{\max} and $AUC_{(0-24h)}$ after single (Cycle 1 Day 1) and multiple doses (Cycle 1 Day 15).

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Pharmacodynamic biomarker:

PD data were summarized based on the Safety Analysis Set who also had at least 1 evaluable/technically-adequate PD data pretreatment and post treatment assessment. Recorded values (and change if necessary) were summarized by dose group using descriptive statistics.

Safety

Safety analyses were conducted based on the Safety Analysis Set. Only in summarizing DLT data, subjects with less than 75% compliance in Cycle 1 for reasons other than the toxicity of the study drug and who discontinued prior to confirmation of tolerability in Cycle 1 were excluded from the analysis of DLT.

The number and the percentage of subjects experiencing any DLT were provided by dose group and overall. Also, the number and the percentage of subjects experiencing particular types of DLTs were provided. The number and the percentage of subjects with treatment-emergent AEs (TEAE) and serious AEs (SAEs) were provided by dose group and overall. This summary was also be provided by system organ class (SOC), preferred term (PT), causal relationship to the study drug, and CTCAE grade. Recorded values (and changes from baseline if necessary) of other safety parameters including laboratory parameters, vital signs, ECG data, and ECOG-PS were summarized by dose group using summary statistics.

Results**Subject Disposition/Analysis Sets**

Nine subjects were entered into the study, 3 in the 20-mg QD group and 6 in the 24-mg QD group, and all received at least 1 dose of study drug. All 9 subjects completed Cycle 1 (DLT monitoring period). The median number of cycles was 2.0 (range: 1 to 6) in the 20-mg QD group and 7.0 (range: 2 to 19) in the 24-mg QD group. Afterwards, all 9 subjects were discontinued from the study. All of the 9 enrolled subjects were included in both the Safety Analysis Set and the PK Analysis Set.

Efficacy

Based on the investigator assessment, 1 of 9 subjects (11.1%) had a best overall response of PR (leiomyosarcoma, 24-mg QD group). Five subjects (55.6%) had SD, and 3 subjects (33.3%) had PD. No subject had a best overall response of CR. The objective response rate (CR + PR) was 11.1% (95% CI: 0.3, 48.2) overall, 0% in the 20-mg QD group, and 16.7% (95% CI: 0.4, 64.1) in the 24-mg QD group. The disease control rate (CR + PR + SD) was 66.7% (95% CI: 29.9, 92.5) overall, 33.3% (95% CI: 0.8, 90.6) in the 20-mg QD group, and 83.3% (95% CI: 35.9, 99.6) in the 24-mg QD group.

Pharmacokinetics

Maximum plasma concentrations of lenvatinib were typically observed 2 hours after first or multiple doses. Exposure, as measured by C_{\max} , $AUC_{(0-24h)}$, $AUC_{(0-t)}$, $C_{ss,\max}$, and $AUC_{(0-\tau)}$, for lenvatinib appeared to increase with dose escalation. Plasma trough concentrations of lenvatinib on Day 8, Day 15 of Cycle 1, and Day 15 of Cycle 2 after multiple doses remained at almost the same level. Plasma concentration of lenvatinib accumulated after repeated dosing, with the mean accumulation index (R_{ac} calculated from C_{\max} and AUC) ranging from 1.27 to 1.44.

Pharmacodynamics

Plasma VEGF level tended to increase in subjects at Days 8 and 15 of Cycle 1. Mean changes in VEGF from baseline at Day 8 and Day 15 of Cycle 1 were 253.43% and 365.39%, respectively. In other PD biomarkers, there were no notable trends in mean and median data.

Safety

No DLTs were reported in either the 20-mg or 24-mg QD group. The 24-mg QD dose was determined to be tolerable, since no DLTs were reported.

In the Safety Analysis Set, all 9 subjects experienced at least 1 TEAE and all 9 subjects (100.0%) had at least 1 TEAE reported to be related to study treatment. The most frequently observed TEAEs were thrombocytopenia, blood thyroid stimulating hormone increased, and hypertension (8 subjects each, 88.9%), followed by leukopenia, proteinuria, and headache (7 subjects each, 77.8%). The most frequently observed treatment-related TEAEs were thrombocytopenia, blood thyroid stimulating hormone increased, and hypertension (8 subjects each, 88.9%), followed by proteinuria and headache (7 subjects each, 77.8%).

There were no Grade 4 TEAEs. The Grade 3 TEAEs observed were neutropenia (3 subjects, 33.3%), blood cholesterol increased (2 subjects, 22.2%), weight decreased, diarrhoea, hypertension, hypertriglyceridaemia, leukopenia, anaemia, lymphopenia and proteinuria (1 subject each, 11.1%). All of these Grade 3 TEAEs were considered by the investigator to be related to study drug. None of these TEAEs led to study drug discontinuation or withdrawal from the study.

No deaths were reported during the study. One subject (11.1%) in the 24-mg QD group experienced a treatment-emergent SAE. The non-fatal SAE, Grade 3 diarrhoea was reported as possibly related to study drug, from which the subject recovered.

TEAEs leading to study drug withdrawal occurred in 1 subject (arthralgia of Grade 1 and palmar-plantar erythrodysesthesia syndrome of Grade 2) in the 24-mg QD group. This subject with melanoma experienced palmar-plantar erythrodysesthesia syndrome (Grade 2, from Day 12 of Cycle 2) and arthralgia (Grade 1, from Day 16 of Cycle 6) and discontinued from the study due to the TEAEs at Day 28 of Cycle 8. TEAEs leading to study drug dose reduction occurred in 2/9 subjects (22.2%): 1 subject with sarcoma (proteinuria of Grade 3) in the 20-mg QD group at Cycle 2 and 1 subject with leiomyosarcoma (stomatitis of Grade 2 and oropharyngeal pain of Grade 2) in the 24-mg QD group at Cycle 5. TEAEs leading to study drug interruption occurred in 6/9 subjects (66.7%): 1/3 subject (33.3%) in the 20-mg QD group and 5/6 subjects (83.3%) in the 24-mg QD group. The most frequently occurring TEAEs leading to study drug interruption were proteinuria (3 subjects), hypothyroidism, abdominal pain upper, malaise, hypoalbuminaemia, and oedema peripheral (2 subjects each). The protocol allowed dose interruption and reduction when clinically necessary regardless of severity of AEs. All but 2 adverse events (Subject PPD Grade 3 blood cholesterol increased and Subject PPD Grade 3 diarrhoea) were Grade 1 or Grade 2.

Overall (N=9), the highest incidence of treatment-emergent markedly abnormal laboratory values was observed for urine protein (7 subjects, 77.8%), followed by leukocytes, neutrophils, and cholesterol (4 subjects each, 44.4%).

Eight subjects (88.9%) experienced hypertension as a TEAE (2/3 subjects [66.7%] in the 20-mg QD group and 6/6 subjects [100.0%] in the 24-mg QD group). Grade 3 hypertension was reported in only 1 subject (24-mg QD group). All of these events were managed with antihypertension medications and assessed as nonserious. No subject discontinued the study drug administration, or required dose reduction and interruption of study drug, due to hypertension.

There were no changes of clinical importance in ECG parameters and ECOG-PS.

Conclusions

The 24-mg dose of lenvatinib was determined to be tolerable when administered orally on a once daily continuous dose schedule in Japanese subjects with solid tumor.

The adverse events observed are consistent with the VEGF targeted therapy profile and are manageable with dose reductions and interruptions.

Date of Report

27 Jan 2014