2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Lenvatinib hard capsules	Referring to Module 5 of the Dossier Volume: Page:	
Name of Active Ingredient: Lenvatinib 4-[3-Chloro-4-(N'-cyclopropyl ureido) phenoxyl]- 7-methoxy quinoline-6-carboxamide methanesulfonate (lenvatinib mesilate)		

Study Title:

An Open-Label, Multicenter Phase 1b/2 Study of E7080 Alone, and in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment

Investigators/Sites:

Four sites. One site in the United Kingdom and 3 sites in the United States.

Publication (Reference):

Molina AM, Hutson TE, Larkin J, Gold AM, Wood K, Carter D, et al. A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC). Cancer Chemother Pharmacol. 2014;73(1):181–9.

Study Period:

12 Aug 2010 (first subject provided informed consent) through 13 Jun 2014 (data cutoff for primary endpoint analysis)

Phase of Development:

Phase 1b part of this Phase 1b/2 protocol

Objectives (Phase 1b):

Primary

- To determine the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD), and establish the recommended Phase 2 (RP2) dose for lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma (RCC).

Secondary

- To determine the tolerability and safety profile of lenvatinib in combination with everolimus.
- To assess pharmacokinetic (PK) and pharmacodynamic (PD) relationship of lenvatinib as combination therapy.

Exploratory

- To assess the best overall response (BOR).

Methodology

This was a multicenter, open-label, Phase 1b/2 study of lenvatinib administered alone and in combination with everolimus in subjects with unresectable advanced or metastatic RCC following 1 prior vascular endothelial growth factor (VEGF)-targeted treatment. The study consisted of 2 parts: Phase 1b and Phase 2. Phase 1b included a Pretreatment Phase, a Treatment Phase, and an Extension Phase.

Phase 1b: Dose escalation was performed to determine the MTD of the combination, cohort expansion to 10 subjects was performed to confirm the MTD, and the dose for lenvatinib in combination with everolimus to use in Phase 2 was recommended (RP2 dose): ie, 18 mg/day lenvatinib + 5 mg/day everolimus was confirmed to be the MTD and the RP2 dose for Phase 2 Treatment Arm A. Once the recommendation was made, enrollment in Phase 2 began. Subjects who received at least 1 dose of study treatment in Phase 1b were not permitted to participate in the Phase 2 part of the study.

Number of Subjects (Planned and Enrolled)

The number of subjects planned was between 3 and 28 with unresectable advanced RCC or metastatic RCC. A total of 28 subjects signed informed consent and 20 subjects were enrolled and administered study medication.

Diagnosis and Main Criteria for Inclusion

Men and women at least 18 years of age with a histologically confirmed diagnosis of RCC, documented evidence of unresectable advanced or metastatic disease, disease progression after prior VEGF-targeted treatment, and Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 were eligible.

Test Treatment - Dose, Mode of Administration, and Batch Numbers

Lenvatinib was provided as 1-mg, 4-mg, and 10-mg capsules. Everolimus was provided as 5-mg tablets. Lenvatinib capsules were to be self-administered orally by the subjects preferably in the morning (consistently either with or without food) at doses of 12 mg, 18 mg, or 24 mg once daily in continuous 28-day treatment cycles. Everolimus tablets were also self-administered orally as 5 mg tablets in continuous 28-day cycles. Dose reduction, interruption, or ultimate discontinuation was possible for all subjects who experienced lenvatinib-everolimus combination therapy-related toxicity.

Lenvatinib Batch/Lot Nos.:

1-mg capsules: P9X007ZZA, P92016ZZB

4-mg capsules: P16004ZZA, P9X008ZZA, P9X009ZZB, P09012ZZA, P1X042ZZA, P93012ZZB

10-mg capsules: P9X010ZZB, P9X012ZZA, P14017ZZA, P14018ZZA, P1Y014ZZA, P22012ZZA, P93014ZZC

Everolimus Batch No.:

5-mg tablets: F0003, F0006, F0008, F0011, F0012, S0013A, S0021

Duration of Treatment

Subjects received study treatment until disease progression, development of unacceptable toxicity, or withdrawal of consent.

Assessments

Efficacy

Preliminary efficacy as BOR was assessed by RECIST v1.1 in subjects in the Safety Analysis Set.

Pharmacokinetics

Blood samples for determination of plasma concentrations of lenvatinib and blood concentrations of everolimus were collected from all subjects. Most subjects had 6 samples taken over 3 cycles of treatment (ie, sparse sampling). Sparse PK sampling was conducted immediately prior to and at any time in between 2 to 8 hours postdose on Day 1 of Cycles 1, 2, and 3. A population PK model for lenvatinib was developed using program NONMEM. The model was parameterized in terms of clearance and volume of distribution.

Safety

Safety was assessed by the monitoring and recording of all adverse events (AEs) including all Common Terminology Criteria for Adverse Events (CTCAE) grades (for both increasing and decreasing severity) and serious AEs (SAEs), regular monitoring of hematology, clinical chemistry, and urinalysis, regular measurement of vital signs, electrocardiograms (ECGs), and Multiple Gated Acquisition (MUGA) scans. A committee met after at least 3 subjects in a given cohort had completed 28 days of Cycle 1 treatment to review data and determine whether escalation (or de-escalation) to the next dosing cohort should occur. The cohort's data were then assessed for DLT criteria as defined per protocol and a decision was made whether to enroll additional subjects and at what dose level. The participants involved in the Dose Escalation Committee and Cohort Review Meetings included the active principal investigators, any subinvestigators, the study nurse, and the study coordinator. The highest dose level resulting in 0 or 1 DLT in 6 subjects was to be considered the MTD.

Bioanalytical Methods

Lenvatinib in plasma and everolimus in blood were quantified using validated high performance liquid chromatography-tandem mass spectroscopy methods.

Statistical Methods

Efficacy Analysis

Best overall response was summarized and listed by cohort based on the Safety Analysis Set.

Safety Analysis

Electrocardiogram findings and the incidence of AEs and SAEs were summarized. Laboratory test results, vital signs, and MUGA Scans (Left Ventricular Ejection Fractions), and their changes from baseline, were summarized using descriptive statistics. Abnormal values were flagged.

Results

Subject Disposition/Analysis Sets

A total of 20 subjects were enrolled in 3 cohorts: 7 in Cohort 1 (lenvatinib 12 mg + everolimus 5 mg), 11 in Cohort 2 (lenvatinib 18 mg + everolimus 5 mg), and 2 in Cohort 3 (lenvatinib 24 mg + everolimus 5 mg). All subjects in each treatment cohort were administered study medication. At the time of data cutoff, all subjects had discontinued treatment with study medication. Of these, 12 subjects (60%) had discontinued due to "study completion" as a result of disease progression, 4 had discontinued due to AEs, 1 subject withdrew consent, and 1 discontinued by choice. The reason for discontinuation was given as clinical progression for the remaining 2 subjects. At data cutoff, 7 subjects (35%) who had discontinued study medication remained in the study for follow-up.

All 20 subjects who received at least 1 dose of study treatment were included in the Safety Analysis Set.

Efficacy

- Efficacy was an exploratory objective in this Phase 1b MTD finding study. Strong evidence of efficacy was observed in this population (20 subjects) with advanced unresectable or metastatic RCC in terms of 1 CR and 5 PR.
- The BOR was 28.6% in Cohort 1 (2 PR) and 36.4% in Cohort 2 (1 CR+3 PR). Additional 9 subjects had a BOR of SD.
- Median PFS was 330 days or 10.9 months (95% CI; 157–446) for both Cohorts 1 and 2.

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics/Pharmacogenetics

Population PK analysis was performed using the PK data collected from sparse PK sampling. The PK concentration data from this study were pooled with data from other lenvatinib studies for population PK analysis and the PK and PK/PD results are reported in a separate report.

Safety

- Based on assessment of DLTs, the MTD and RP2 dose of combination was established at lenvatinib 18 mg plus everolimus 5 mg, administered orally once daily. This is the dose that was used in the Phase 2 extension of this study.
- Subjects in Cohort 1 and Cohort 2 received a median of 8 and 12 cycles of treatment respectively; however both subjects in Cohort 3 (lenvatinib 24 mg + everolimus 5 mg) received study medication only during the first cycle of treatment due to DLTs.
- TEAEs occurred in all study subjects, and majority of the subjects had Grade 3 AEs (100% in Cohort 1, 91% in Cohort 2, and 50% in Cohort 3). Grade 4 TEAEs were reported in only 2 of all 20 subjects in this study, and there were no Grade 5 (fatal) AEs.
- Overall, the most frequent individual Grade 3 TEAE was hyponatremia in 5 subjects (2 in Cohort 1 and 3 in Cohort 2). Other Grade 3 TEAEs reported in both Cohort 1 and Cohort 2 were diarrhea (3 subjects), dyspnea (4 subjects), fatigue (4 subjects), acute renal failure (3 subjects), and peripheral edema (2 subjects). Both Grade 4 TEAEs (hyperkalemia and dyspnea) occurred in Cohort 2.
- There were 2 deaths within 30 days after last dose of study medication, and both were considered by the investigator to be due to disease progression. Nonfatal SAEs were reported in 14 subjects, 6 (85.7%) in Cohort 1 and 8 (72.7%) in Cohort 2.
- The most common treatment-related TEAE was fatigue, followed by stomatitis, diarrhea, nausea and hypertension. The most common Grade 3 or 4 treatment-related TEAEs were hypertriglyceridemia, proteinuria and diarrhea.
- Dose reductions for lenvatinib were required in 10 (50%) subjects, most notably in Cohort 2 (n=7; 63.6%).
- The study medication was discontinued due to AEs in 5 subjects in Cohort 2 and in 1 subject in Cohort 3, but none in Cohort 1.

Date of Report

13 OCT 2015