# 2   STUDY SYNOPSIS

| Name of Company:<br>Eisai Inc. | INDIVIDUAL STUDY TABLE | (For National Authority Use Only) |
|---|---|---|
| Name of Finished Product:<br>Lenvatinib hard capsules | Referring to Module 5<br>of the Dossier | |
| Name of Active Ingredient:<br>Lenvatinib (E7080) | Volume:          Page: | |

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| **Study Title**<br>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**<br>Phase 2:  A total of 37 sites in 5 countries (Czech Republic [5 sites], Poland [4 sites], Spain [4 sites], the United Kingdom [11 sites], and the United States [13 sites]). |
| **Publication (Reference)**<br>Molina AM, Hutson TE, Larkin J, Gold AM, Wood K, Carter D, Motzer R, Michaelson MD.  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;73:181–189.<br><br>Motzer R, Hutson T, Glen H, Michaelson D, Molina A, Eisen A, et al. Randomized phase II, three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC). Presentation at the 2015 ASCO Annual Meeting. Chicago (IL) J Clin Oncol 33, 2015 (suppl; abstr 4506). |
| **Study Period**<br>Phase 2:  16 Mar 2012 (first subject provided informed consent) to 13 Jun 2014 (data cutoff date for the primary endpoint) |
| **Phase of Development**<br>Phase 1b/2 (The Phase 2 part of the study is reported in this clinical study report [CSR]) |
| **Objectives (Phase 2)**<br>*Primary*<br><br>• To compare the progression-free survival (PFS) of 1) lenvatinib in combination with everolimus at the recommended Phase 2 (RP2) dose once daily (QD) (Arm A) and 2) single agent lenvatinib 24 mg QD (Arm B) to single agent everolimus 10 mg QD (Arm C) in subjects with unresectable advanced or metastatic renal cell carcinoma (RCC) and disease progression following 1 prior vascular endothelial growth factor (VEGF)-targeted treatment.<br><br>*Secondary*<br><br>• To determine the tolerability and safety profile of lenvatinib in combination with everolimus and of single agent lenvatinib.<br><br>• To compare PFS of Arm A, lenvatinib-everolimus combination therapy to Arm B, single agent lenvatinib.<br><br>• To assess overall survival (OS).<br><br>• To assess objective response rate (ORR: complete response + partial response [CR + PR]); disease control rate (DCR: CR + PR + stable disease [SD]); durable SD (SD ≥23 weeks) and clinical benefit rate (CBR: CR, PR + durable SD rate).<br><br>• To assess pharmacokinetic (PK) profiles (eg, AUC, $C_{max}$) of lenvatinib and everolimus during single agent and combination therapy.<br><br>• To assess PK and pharmacodynamic (PD) relationship of lenvatinib as single agent and combination therapy. |

*Exploratory*

- To identify and explore blood and tumor biomarkers which correlate with efficacy-related endpoints of this study.
- To evaluate role of DNA sequence variability on absorption, distribution, metabolism, excretion (ADME) and susceptibility to adverse events (AEs) of lenvatinib.

**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. The study consisted of 2 parts: Phase 1b and Phase 2. The Phase 2 part of the study is reported in this CSR; Phase 1b is reported separately.

Phase 2 included a Prerandomization Phase, a Randomization Phase, and an Extension Phase. Subjects were randomized into 3 arms to receive: 1) 18 mg/day lenvatinib + 5 mg/day everolimus (RP2 dose; Arm A [combination arm]), 2) lenvatinib 24 mg/day (Arm B [lenvatinib arm]), or 3) everolimus 10 mg/day (Arm C [everolimus arm]). Randomization was stratified by hemoglobin (≤13 g/dL vs >13 g/dL for males and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium levels (≥10 mg/dL vs <10 mg/dL).

**Number of Subjects (Planned and Enrolled)**

Planned: Approximately 150 subjects were planned to be enrolled in Phase 2 part of the study.

Enrolled: A total of 153 subjects were enrolled.

**Diagnosis and Main Criteria for Inclusion**

Eligible subjects had unresectable or advanced RCC, histological or cytological confirmation of predominant clear cell RCC, radiographic evidence of disease progression on or within 9 months of stopping prior therapy, 1 prior VEGF-targeted therapy, and measurable disease according to RECIST 1.1. Other key eligibility criteria included Eastern Cooperative Oncology Group Performance Status (ECOG PS) of ≤1, adequately controlled blood pressure with or without antihypertensive medications, and adequate renal, bone marrow, blood coagulation, liver, and cardiac function.

**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 and everolimus tablets were to be self-administered orally by the subjects preferably in the morning (consistently either with or without food) in continuous 28-day cycles as follows:

- Arm A (combination arm): the RP2 dose of Lenvatinib (18 mg) QD + everolimus (5 mg) QD
- Arm B (lenvatinib arm): Lenvatinib 24 mg QD

Dose interruption, dose reduction, or treatment discontinuation was allowed for subjects who experienced lenvatinib-related toxicity. Subjects in the combination arm who experienced everolimus-related toxicity had dose adjustments in accordance with prescribing information.

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

**Reference Therapy, Dose, Mode of Administration, and Batch Numbers**

Everolimus was provided as 5-mg tablets. In Arm C (everolimus arm), everolimus 10 mg QD was to be self-administered orally by the subjects in the morning (consistently either with or without food) in continuous 28-day cycles. Subjects who experienced everolimus-related toxicity had dose adjustments in accordance with prescribing information.

Everolimus Batch/Lot Nos.:     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**

Tumor assessments using RECIST 1.1 were performed during the Prerandomization Phase and then every 8 weeks (or sooner if there was evidence of progressive disease) from the date of randomization in the Randomization Phase, and in the Extension Phase. Tumor assessments were performed until documentation of disease progression. Subjects who discontinued the study treatment without disease progression in the Randomization Phase had to undergo tumor assessments every 8 weeks in the Randomization Phase, until disease progression was documented or another anticancer therapy was initiated. During the Extension Phase, subjects who discontinued study treatment without disease progression had tumor assessments performed as clinically indicated using the investigator's discretion, following the standard of care at their institution.

Investigator-determined response assessments were performed at each assessment time point.

**Pharmacokinetic Assessments**

Blood samples for determination of plasma concentrations of lenvatinib and blood concentrations of everolimus were collected at protocol-specified time points from all subjects during the Randomization Phase. Most subjects had 6 samples taken over 3 cycles of treatment (ie, sparse sampling). However, between 9 and 12 subjects in each of the 3 treatment arms in Phase 2 participated in an optional substudy where instead of the sparse sampling, intensive sampling was performed (ie, full PK profiling).

**Safety**

Safety was assessed by the monitoring and recording of all AEs and serious AEs (SAEs); regular monitoring of hematology, clinical chemistry, and urine values; and regular measurement of vital signs, electrocardiograms (ECGs), and Multiple Gated Acquisition (MUGA) scans.

**Bioanalytical Methods**

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

**Statistical Methods**

**Primary Efficacy Endpoint**

- Progression-free survival defined as the time from the date of randomization to the date of first documentation of disease progression or death (whichever occurred first) as determined by the investigator using RECIST 1.1.

**Secondary Efficacy Endpoints**

- Overall survival measured from the date of randomization until date of death from any cause.

- Objective response rate defined as the proportion of subjects who had best overall response (BOR) of CR or PR as determined by the investigator using RECIST 1.1.

- Disease control rate defined as the proportion of subjects who had BOR of CR or PR or SD (minimum duration from randomization to SD ≥7 weeks).

- Clinical benefit rate defined as the proportion of subjects who had BOR of CR or PR or durable SD (duration of SD ≥23 weeks).

- Durable SD rate defined as the proportion of subjects with duration of SD ≥23 weeks.

**Analysis Sets**

- Full Analysis Set (FAS) included all subjects randomly assigned to treatment. This was the primary analysis set for efficacy endpoints.

- Phase 2 PK Sub Analysis Set consisted of subjects who participated in the intensive PK sampling portion of Phase 2 of the study.

- Safety Analysis Set included all subjects who received at least 1 dose of the study drug and had at least 1 postbaseline safety evaluation. This was the analysis set for all safety evaluations.

**Sample Size Determination and Statistical Methods**

The planned sample size for the primary analysis required a total of at least 90 PFS events to be observed across all 3 treatment groups, and at least 60 PFS events to be observed for each of the comparisons of the combination versus the everolimus arm, and the lenvatinib versus the everolimus arm. The assumed median PFS for everolimus 10 mg was 5 months based on historical data. Given that there were no prior clinical data available for the combination of lenvatinib plus everolimus, and limited data for lenvatinib alone in the target population, it was appropriate to consider that a HR=0.67 represents a clinically meaningful improvement in PFS. Under the assumption of an exponential event distribution of the time to PFS random variable, this effect translated into median PFS of 7.5 months. The study was designed as a Phase 2 study where a total of 90 PFS events were required to detect a HR of 0.67 with 70% power using an (1-sided) alpha of 0.15 for the comparison of the combination arm (and lenvatinib arm) versus the everolimus arm. An independent statistical review was conducted to ensure that at least 60 PFS events were observed for each of the comparisons of the combination versus the everolimus arm, and the lenvatinib versus the everolimus arm. The actual observed number of PFS events was to be used to calculate the hazard ratio when comparing treatment arms.

**Efficacy Analyses**

All efficacy analyses were based on investigator assessment on the FAS. Primary comparison of PFS was between combination arm and everolimus arm or lenvatinib arm and everolimus arm. Secondary comparison of PFS was between combination arm and lenvatinib arm. There was no prespecified ordering in testing these hypotheses (primary and secondary) and each null hypothesis was tested at a nominal $\alpha$=0.05.

For each treatment comparison (combination arm vs everolimus arm or lenvatinib arm vs everolimus arm), null hypothesis of no difference in PFS was analyzed using the stratified log-rank test with hemoglobin ($\leq$13 g/dL vs >13 g/dL for males; and $\leq$11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium ($\geq$10 mg/dL vs <10 mg/dL) as stratification factors. Median PFS was estimated using the Kaplan-Meier (K-M) product-limit estimates for each arm and the corresponding 2-sided 95% confidence interval (CI) was computed using the Greenwood formula. Hazard ratio (HR) between treatment groups and corresponding 95% CI was estimated using the stratified Cox regression model (stratified by hemoglobin and corrected serum calcium) with treatment as a factor.

Secondary efficacy endpoints: OS analyses were performed using the stratified Cox proportional model used for the primary analysis. Each null hypothesis of no difference in OS was evaluated using the stratified log-rank test, and tested at (2-sided) $\alpha$=0.05. Median OS and its corresponding (2-sided) 95% CI were estimated similarly as for the primary analysis for PFS. ORR, DCR, CBR and durable SD rate were calculated with exact 95% CIs using the method of Clopper and Pearson. Ad-hoc analyses were performed to estimate the crude rate ratio of each treatment comparison and to compute *P* values using the Fisher's exact (2-sided) test.

**Pharmacokinetic Analyses**

Population PK model analysis was performed with sparse sampling PK using data from other lenvatinib studies as appropriate for the population PK model. The population PK analysis and PK/PD results are reported separately.

For the intensive PK sampling substudy, PK parameters were derived using non-compartmental methods for lenvatinib and everolimus during single agent and combination therapy. To assess any drug-drug interaction between lenvatinib and everolimus, the primary PK parameters of lenvatinib and also everolimus from the Phase 2 PK data set were compared graphically and via descriptive statistics between single agent and combined therapy.

**Safety Analyses**

Safety data were summarized using descriptive statistics. Categorical variables were summarized by number and percentage. Continuous variables were summarized using n (number of subjects with available data), mean, standard deviation (SD), median, and range (minimum and maximum) unless otherwise specified. ECG findings and the incidence of AEs and SAEs were summarized. Laboratory test results, vital signs, and left ventricular ejection fractions (from MUGA Scans), and their changes from baseline, were summarized using descriptive statistics.

**Results**

**Subject Disposition/Analysis Sets**

In total, 153 subjects were randomly assigned to the 3 treatment arms: 51 subjects to the combination arm, 52 subjects to the lenvatinib arm, and 50 subjects to the everolimus arm. Mean and median age were well balanced

among the treatment arms. The treatment arms also were well balanced across parameters, including the independent prognostic factors in RCC: ECOG PS, corrected serum calcium (stratification factor), and hemoglobin level (stratification factor). All 153 subjects were treated. Data cutoff occurred as planned on 13 Jun 2014 following the occurrence of 101 PFS events among the 3 treatment arms, 63 PFS events in the combination versus everolimus arm, and 75 PFS events in the lenvatinib versus everolimus arm.

At the time of data cutoff, a higher number of subjects in the combination arm (13; 25.5%) were still on treatment than in the lenvatinib or everolimus arms (7; 13.5% and 3; 6.0%, respectively). Fewer subjects ended treatment due to disease progression in the combination arm (19; 37.3%) and lenvatinib arms (29; 55.8%) than in the everolimus arm (35; 70.0%).

As of the date of data cutoff, 69 (45.0%) subjects (31 in the combination arm, 23 in the lenvatinib arm, and 15 in the everolimus arm) remained in the study, including 23 (15.0%) subjects who were still receiving study treatment.

All 153 subjects who were randomized and treated were included in the FAS and the Safety Analysis Set.

**Efficacy**

- In patients with mRCC and disease progression following 1 prior VEGF-targeted treatment, the combination of lenvatinib 18 mg with everolimus 5 mg demonstrated statistically significant and clinically meaningful improvement in PFS compared with the everolimus arm (median 14.6 months vs 5.5 months, respectively).

- The combination showed improvement in PFS over everolimus for all subgroups analyzed (HRs range from 0.14 to 0.61).

- The combination arm showed an impressive, statistically significant (*P<0.0001*) and clinically meaningful improvement in ORR (43.1%) compared with both single agent arms (26.9% for the lenvatinib arm, and 6.0% for the everolimus arm).

- The combination arm showed a trend toward prolonged survival (HR = 0.55) compared with the everolimus arm that reached statistical significance (*P=0.0242*) in the updated OS analysis based on a 10 Dec 2014 data cutoff (HR = 0.51). Median survival was 25.5 months for the combination arm and 15.4 months for the everolimus arm.

- Lenvatinib also showed a statistically significant improvement (*P*=0.0479) in PFS (median 7.4 months) compared with everolimus.

- The ORR for the lenvatinib arm versus the everolimus arm was statistically significant (*P=0.0067*) favoring the lenvatinib arm.

**Pharmacokinetics (Phase 2 PK Sub-analyses)**

- Based on the dose-normalized $C_{max}$ and $AUC_{(0-24)}$, the mean lenvatinib $C_{max}$ was similar between the combination and the lenvatinib arms while the mean systemic exposure as measured by $AUC_{(0-24)}$ was approximately 20% lower in the combination arm compared to the lenvatinib arm.

- Based on the dose-normalized $C_{max}$ and $AUC_{(0-24)}$, the mean everolimus Cmax was approximately 30% greater in the combination arm compared to the everolimus arm. A similar increase was observed with the mean $AUC_{(0-24)}$ being approximately 50% higher in the combination arm compared to the everolimus arm. These results should be viewed with caution given the small number of subjects in each treatment arm.

- In conclusion, the combination of lenvatinib and everolimus has shown substantial evidence of superior efficacy in terms of improved PFS, higher ORR and longer OS (as per the updated data) compared with standard everolimus in treatment of subjects with unresectable advanced or metastatic RCC who had progressed following 1 prior VEGF-targeted treatment.

The results of the population PK and PK/PD model are reported in a separate report.

**Safety**

- Subjects in the combination arm received a median of 9.0 cycles of treatment with approximately 75% of the intended dose of lenvatinib and 94% of the intended dose of everolimus, achieving longer exposure compared with subjects on the lenvatinib (median of 8.5 cycles) or everolimus (median of 5.0 cycles) arms.

- The percentage of subjects with lenvatinib dose reduction and/or dose interruption (as an action taken on the Adverse Event CRF) was similar in the combination and lenvatinib arms (84.3% and 78.8%, respectively). The percentage of subjects with study treatment discontinuation was similar in both lenvatinib containing arms (23.5% for the combination and 25.0% for the lenvatinib arm).

- The AE profile for lenvatinib was as expected for this class of compounds and consistent with the lenvatinib label and the clinical program as a whole. Similarly, the AE profile of everolimus was consistent with its label.
- Diarrhea (84%) was the most frequently reported TEAEs overall across the 3 treatment arms (>30% of subjects in any treatment arm) and occurred most often in the combination arm. Other common TEAEs in the combination arm included decreased appetite (51%), fatigue (47%), vomiting (45%), nausea (41%), hypertension (41%), cough (37%), hypertriglyceridemia (35%), hypercholesterolemia (33%), and weight decreased (31%). These events are consistent with the safety profile of lenvatinib.
- Grade 3 AEs were reported in 70.6%, 82.7%, and 52.0% subjects in the combination, lenvatinib, and everolimus arms, respectively. Substantially fewer Grade 4 events were reported in all 3 treatment arms, with similar incidence across the arms (13.7%, 9.6%, and 12.0% in the combination, lenvatinib, and everolimus arms, respectively).
- Grade 3 gastrointestinal (GI) events, including diarrhea and vomiting, occurred at a higher frequency in the combination arm (35.3%) than in the lenvatinib (19.2%) and everolimus (6.0%) arms. In addition, GI SAEs were reported more frequently in the combination (11.8%) than in the lenvatinib (3.8%) and everolimus arms (0%).
- The incidence of nonfatal (ie, other) SAEs in the combination and lenvatinib arms was similar, and was higher compared with the everolimus arm: (52.9% and 50.0% vs 42.0%, respectively).
- Serious renal events were reported with similar frequency in the combination (7.8%) and lenvatinib arms (9.6%), suggesting no increase in renal toxicity when lenvatinib was combined with everolimus.
- The occurrence of serious infections was similar among the combination (9.8%), and everolimus (10.0%) arms, as was the occurrence of serious pneumonitis (2.0% and 6.0% for the combination and everolimus arms, respectively).
- Death due to AEs occurred in 1 (2.0%) subject in the combination arm, 3 (5.8%) subjects in the lenvatinib arm, and 2 (4.0%) subjects in the everolimus arm. When adjusted by treatment duration, the incidence of fatal AEs was 0.03 episodes per subject year (SY) in the combination, 0.09 episodes per SY in the lenvatinib, and 0.08 episodes per SY in the everolimus arm.
- Diarrhea and vomiting were the most frequently reported AEs that led to dose reduction and/or interruption in the combination arm. These events resulted in dose reduction and/or interruption more often in the combination than in the lenvatinib arm: 41.2% vs 28.8%, respectively, for diarrhea and 19.6% vs 5.8%, respectively, for vomiting.
- The percentages of subjects with study treatment discontinuation due to AEs (as an action taken on the Adverse Event page of the CRF) were similar in both the combination and lenvatinib arms (23.5% and 25.0%, respectively) and were approximately 2-fold higher than in the everolimus arm (12.0%).
- The percentage of subjects who had everolimus dose interruptions due to AEs was higher in the combination arm than in the everolimus arm (76.5% vs 54.0%), while the percentage of subjects with everolimus dose reductions was higher in the everolimus arm (26.0%) than in the combination arm (2.0%). The percentage of subjects with study treatment discontinuation due to AEs (as an action taken on the Adverse Event CRF) was higher in the combination arm (23.5%) compared to everolimus arm (12.0%).
- Overall, clinically significant AEs for lenvatinib occurred in 38 subjects (74.5%) in the combination arm, 48 subjects (92.3%) in the lenvatinib arm, and 31 subjects (62.0%) in the everolimus arm, and are consistent with the known safety profile of each drug. The clinically significant AEs, especially the main characteristic toxicities of lenvatinib (hypertension and proteinuria) and everolimus (stomatitis, non-infectious pneumonitis, renal events, and infections) showed that the incidence or severity of these toxicities was not worsened when administered in combination compared to the individual/monotherapy treatments.

**Conclusions**

Although this study was not designed as a formal Phase 3 study, it does provide substantial evidence of the efficacy of the combination when compared to the approved comparator, everolimus. The results are statistically significant, clinically meaningful and internally consistent as demonstrated by the robust statistical superiority in all subgroups for PFS and ORR and further supported by a trend in OS that reached nominal significance in a post-hoc update analysis. The safety profile of the combination showed increase in GI (diarrhea, vomiting) events relative to the single agents. Importantly, significant AEs known to occur with each single agent did not increase above the single agent frequency or severity in the combination arm.

**Date of Report**

13 OCT 2015