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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	
Name of Active Ingredient: Lenvatinib (E7080)	Volume: Page:	

Study Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer

Investigators/Sites

Multicenter: 117 sites in the European Union (EU), North America, Asia Pacific, Japan, and Latin America [redacted]

Publication (Reference)

None

Study Period

05 Aug 2011 to 15 Nov 2013 (date of data cutoff for the primary analysis)

Phase of Development

Phase 3

Objectives

Primary

- To compare the progression-free survival (PFS) of subjects with ^{131}I-refractory differentiated thyroid cancer (RR-DTC) and radiographic evidence of disease progression within the prior 12 months treated with lenvatinib versus placebo

Secondary

- To compare overall response rate (ORR) (complete and partial responses [CR and PR]) of subjects treated with lenvatinib versus placebo
- To compare overall survival (OS) of subjects treated with lenvatinib versus placebo
- To compare safety and tolerability of lenvatinib versus placebo
- To assess the pharmacokinetic (PK) profile of lenvatinib in subjects with RR-DTC

Exploratory

- To compare disease control rate (DCR) (CR, PR, or stable disease [SD]), clinical benefit rate (CBR) (CR, PR + durable SD), and durable SD (duration of SD ≥23 weeks) of subjects treated with lenvatinib versus placebo
- To assess safety and efficacy of lenvatinib administered in the Optional Open Label (OOL) Lenvatinib Treatment Period
- To identify and validate blood and tumor biomarkers that correlate with efficacy-related endpoints of this study
- To identify and validate DNA-sequence variants in genes influencing lenvatinib absorption, distribution, metabolism, excretion (ADME)

Methodology

Study E7080-G000-303 was a multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of lenvatinib in adult subjects who had RR-DTC and had radiographic evidence of disease progression within the prior 12 months (confirmed by independent imaging review [IIR]). Subjects who received 0 or 1 prior VEGF/VEGFR-targeted therapy were eligible for enrollment. Subjects were randomly assigned in a 2:1 ratio to receive lenvatinib 24 mg or placebo, administered continuously as once daily oral dosing. A treatment cycle was defined as 28 consecutive days. Randomization was stratified by geographic region (Europe, North America, and Other), age group (≤65 or >65 years), and prior VEGF/VEGFR-targeted therapy (0 or 1).

The IIR was responsible for 1) radiographic eligibility confirmation (radiographic evidence of disease progression within the prior 12 months and the presence of at least 1 target lesion per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), 2) confirmation of progressive disease (PD) while on study (required before a subject could discontinue treatment in the Randomization Phase), and 3) formal efficacy reads by 2 radiologists, with adjudication where necessary, followed by a medical oncology review.

The study was conducted in 3 phases: a Prerandomization Phase, a Randomization Phase, and an Extension Phase.

- The **Prerandomization Phase** included a Screening Period to establish subject eligibility and a Baseline Period to establish disease characteristics prior to treatment and to confirm eligibility.
- The **Randomization Phase** was the blinded study treatment phase, which began when the first subject was randomly assigned to treatment and ended at the time of the data cutoff for the primary study analysis (214 progression events or deaths prior to disease progression). Subjects received blinded study drug until documentation of disease progression (confirmed by IIR), development of unacceptable toxicity, or withdrawal of consent. Subjects who discontinued treatment due to disease progression (confirmed by IIR) entered the Extension Phase. Subjects who discontinued treatment for any reason other than disease progression were followed in the Randomization Phase until disease progression or start of another anticancer treatment; these subjects then entered the Extension Phase for survival follow-up. All subjects on treatment at the time of the data cutoff for the primary analysis entered the Extension Phase.
- The **Extension Phase** included an OOL Lenvatinib Treatment Period and a Follow-up Period. Subjects in the placebo arm who had disease progression confirmed by IIR could request to enter the OOL Lenvatinib Treatment Period and receive lenvatinib treatment. After the primary analysis was completed, subjects treated with lenvatinib who had not experienced disease progression could request to continue open-label lenvatinib at the same dose, according to the clinical judgment of the investigator. Subjects taking placebo at the time of unblinding could be treated with lenvatinib in the OOL Lenvatinib Treatment Period immediately or at the time of progression after a documented discussion of the risks and benefits with the investigator. Qualified subjects received lenvatinib treatment in the OOL Lenvatinib Treatment Period until disease progression (investigator's assessment), development of intolerable toxicity, or withdrawal of consent.

  Subjects who had disease progression during the Randomization Phase and did not enter the OOL Lenvatinib Treatment Period and all subjects who discontinued lenvatinib treatment entered the Follow-up Period. Subjects were followed for survival, and all anticancer treatments were recorded until the time of death. The Follow-up Period will continue as long as study subjects are alive or until discontinuation of survival follow-up by the sponsor.

Number of Subjects (Planned and Enrolled)

Planned: Approximately 360 subjects with RR-DTC and radiographic evidence of disease progression within the prior 12 months

Enrolled: 392

Diagnosis and Main Criteria for Inclusion

- Males or females age ≥18 years at the time of informed consent
- Histologically or cytologically confirmed diagnosis of one of the following DTC subtypes: Papillary thyroid cancer (PTC) or follicular thyroid cancer (FTC)
- Measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)

and confirmed by central radiographic review

- ^{131}I-refractory/resistant disease
- Evidence of disease progression within 12 months prior to signing informed consent (+1 month screening window)
- Prior treatment with 0 or 1 VEGF or VEGFR-targeted therapy
- Adequate renal, liver, bone marrow, and blood coagulation function, as defined in the protocol.

Main Criteria for Exclusion

- Anaplastic or medullary carcinoma of the thyroid
- 2 or more prior VEGF/ VEGFR-targeted therapies
- Received any anticancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug.

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

Lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule) continuous QD oral dosing.

Batch No.: 4-mg capsules: [redacted]

10-mg capsules: [redacted]

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

Matching placebo capsules continuous QD oral dosing.

Batch No.: 4-mg capsules: [redacted]

10-mg capsules: [redacted]

Duration of Treatment

Subjects took blinded study drug once daily until confirmed disease progression (by IIR), 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 from the date of randomization in the Randomization Phase and every 12 weeks in the Extension Phase. Copies of tumor assessment scans were sent to an imaging core lab for Independent Eligibility Confirmation, as well as IIR which served as the basis for the primary analysis. Subjects were required to have independent confirmation of disease progression before discontinuing treatment in the Randomization Phase and having the option of entering the OOL Lenvatinib Treatment Period if they had been randomized to placebo. Investigator-determined response assessments were performed at each assessment time point.

Subjects who discontinued treatment without disease progression in the Randomization Phase continued to undergo tumor assessments every 8 weeks in the Randomization Phase, until disease progression was documented or another anticancer therapy was initiated.

Pharmacokinetic Assessments

Blood samples for determination of plasma concentration versus time profiles of lenvatinib were collected from all subjects during the Randomization Phase.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood samples were collected during the Randomization Phase for biomarker discovery and validation to identify blood or tumor biomarkers that might be important for predicting subject response to lenvatinib as determined by evaluation of primary or secondary efficacy endpoints.

A blood sample was collected during the Randomization Phase for pharmacogenomic analysis of DNA to identify possible gene mutations associated with lenvatinib ADME.

Pharmacokinetic/pharmacodynamic relationships (dose and/or exposure effect relationships) were explored for

effects of lenvatinib on tumor response (PR, CR, SD) and PFS (based on RECIST 1.1), OS, AEs/dose reductions and the interrelationships.

Archived, fixed tumor tissue was collected (if available) for identification of possible somatic gene mutations including BRAF V600E as well as other genes that may be important in the development and progression of DTC. Planned assessments included gene-expression profiling (GEP), proteomics, or immunohistochemical (IHC) assays, depending on the amount of tumor tissue available for analysis. Planned analyses were limited to correlations relevant to DTC and clinical outcomes related to treatment with lenvatinib.

Safety

Safety was assessed by the monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs); regular monitoring of hematology, clinical chemistry, and urine values; physical examinations; and regular measurement of vital signs, electrocardiograms (ECG), and echocardiograms.

Bioanalytical Methods

Lenvatinib was quantified using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method.

Statistical Methods

Study Endpoints

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 blinded IIR conducted by the imaging core laboratory using RECIST 1.1

Secondary Efficacy Endpoints

- Objective response rate, defined as the proportion of subjects who had best overall response (BOR) of CR or PR as determined by blinded IIR using RECIST 1.1
- Overall survival measured from the date of randomization until date of death from any cause.

Exploratory Efficacy Endpoints

- Disease control rate, defined as the proportion of subjects who had BOR of CR, PR, or SD. Stable disease had to be achieved ≥7 weeks after administration of the first dose of study drug to be considered BOR. For the OOL Lenvatinib Treatment Period, stable disease had to be achieved ≥7 weeks after Cycle 1 Day 1 to be considered BOR.
- Clinical benefit rate, defined as the proportion of subjects who had BOR of CR, PR, or durable SD (duration ≥23 weeks).
- Durable SD rate, defined as the proportion of subjects with duration of SD ≥23 weeks.

Analysis Populations

- Full Analysis Set (Intent-to-Treat Analysis Set) included all randomized subjects. This was the primary analysis set for efficacy endpoints.
- Per Protocol Analysis Set included those subjects who were randomized and received at least 1 dose of the assigned study drug and had no major protocol deviations. The population included those who had both baseline and at least 1 postbaseline tumor assessment or those who died within 125 days after randomization in the absence of postbaseline tumor assessment. This was the secondary analysis set for all tumor response related efficacy endpoints.
- Safety Analysis Set included all subjects who received any amount of the study drug or placebo in the Randomization Phase. This was the analysis set for all safety evaluations.

Efficacy Analyses

The null hypothesis of no difference in the PFS between lenvatinib versus placebo was tested using the stratified log-rank test with 2-sided alpha level of 0.01 stratified by region (Europe, North America, Other), age group (≤65, >65years), and prior VEGF/VEGFR therapy (0, 1). This was the primary test for PFS, which was performed when the target number of 214 events (progression or deaths prior to disease progression) occurred. The calculation of PFS as the primary analysis was based on disease progression as determined by tumor

assessments performed by IIR. The unstratified log-rank test performed as supportive.

The Cox proportional hazards model was used to estimate the hazard ratio (HR) of lenvatinib versus placebo for PFS and its 95% and 99% confidence intervals (CIs) (stratified by region, age, and prior VEGF/VEGF-targeted therapy). The median and quartiles for PFS and the PFS rates at 6, 12, 18, and 24 months were calculated using the Kaplan-Meier (K-M) product-limit estimates for each treatment arm, and presented with 2-sided 95% CIs.

For the secondary endpoint of ORR, the difference between lenvatinib versus placebo was tested using the Cochran-Mantel-Haenszel (CMH) test at a 2-sided significance level of 0.05, stratified by region, age, and prior VEGF/VEGFR therapy.

The OS endpoint was confounded by the fact that qualified placebo subjects with confirmed disease progression had the option to crossover to lenvatinib treatment in the OOL Treatment Phase. To correct the bias and estimate the true treatment effect on OS, the rank preserving structural failure time (RPSFT) model was planned to estimate OS curves (including OS rates at 12, 18, and 24 months) as the primary analysis for survival. The adjusted K-M curves for the placebo arm with adjusted HR and 95% CI were estimated. Overall survival curves were also estimated using the K-M method and compared between treatment arms using the stratified log-rank test. The Cox proportional hazards model was used to estimate the HR of lenvatinib versus placebo for OS and its 95% CI (stratified by the factors used for the PFS analysis).

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. Laboratory test results were summarized using 3 categories, hematology, liver and renal, and other clinical chemistry. Hematology and clinical chemistry parameters that were graded by Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0) were summarized by CTCAE grade. Shifts from baseline to the worst CTCAE grade were tabulated.

Determination of Sample Size

Approximately 360 subjects were planned to be enrolled, based on the ability to detect an HR of 0.5714 (75% improvement in PFS), with 90% power at a 2-sided Type 1 error rate of 0.01 and an enrollment rate of approximately 20 subjects per month.

A total of approximately 214 PFS events (progression, or deaths in the case of no progression) were required for the final analysis of PFS. The 214 PFS events were estimated to occur approximately 29 months (18 months, enrollment period; 11 months, follow-up period) after the start of the Randomization Phase.

Interim Analyses

No interim analyses to stop the trial for superior efficacy based on PFS were planned. Periodic safety monitoring was conducted by the Data Monitoring Committee (DMC).

Results

This clinical study report (CSR) presents results of the primary efficacy analysis and other efficacy and safety results obtained during the Randomization Phase. The results obtained during the OOL Lenvatinib Treatment Period are presented in the E7080-G000-303 OOL CSR.

Subject Disposition/Analysis Sets

In total, 392 subjects were randomly assigned to treatment across 117 study sites worldwide. Data cutoff occurred on 15 Nov 2013 following the occurrence of 214 progression events or deaths prior to disease progression. This CSR presents the results of the primary study analysis.

At the time of data cutoff, treatment was ongoing for 122 (46.7%) lenvatinib-treated subjects and 8 (6.1%) placebo-treated subjects. Disease progression occurred in 94 (36.0%) subjects in the lenvatinib arm and 119 (90.8%) subjects in the placebo arm. Treatment was discontinued prematurely for 45 (17.2%) subjects in the lenvatinib arm and 4 (3.1%) subjects in the placebo arm. The most frequent reason for premature discontinuation in both treatment arms was AEs: 37 (14.2%) subjects in the lenvatinib arm and 3 (2.3%) subjects in the placebo arm.

All 392 subjects randomized to treatment in the study (261 in the lenvatinib arm and 131 in the placebo arm) were included in both the Full Analysis Set and the Safety Analysis Set. The Per Protocol Analysis Set comprised 383/392 (97.7%) subjects, 256/261 (98.1%) subjects in the lenvatinib arm and 127/131 (96.9%)

subjects in the placebo arm.

Efficacy

- Based on IIR assessments using the Full Analysis Set, the median PFS was 18.3 months for lenvatinib compared with 3.6 months for placebo, with an HR of 0.21 (99% CI: 0.14, 0.31), as estimated from the stratified Cox proportional hazard model. The difference in PFS between the lenvatinib and placebo arms was statistically significant (P<0.0001) using both a stratified and unstratified log-rank test.
- The results of the primary efficacy analysis were fully supported by the results of the analysis with the Per Protocol Analysis Set. The median PFS and 95% CI were the same for the 2 analysis sets. The results of the 3 planned sensitivity analyses were consistent with the primary PFS analyses (Sensitivity Analysis A [all events and deaths], Sensitivity Analysis B, [investigators' assessments], and Sensitivity Analysis C [uniform scheduled date of assessment]. The log-rank tests all showed a statistically significant difference between lenvatinib treatment and placebo (P<0.0001). The HRs for all the analyses were comparable (0.21 to 0.24).
- The median PFS was longer with lenvatinib treatment compared with placebo for all of the subgroups evaluated (age group [≤65, >65 years], sex, race, prior VEGF/VEGFR-targeted therapy [0, 1], region [Europe, North America, Other], histology [papillary, follicular], and TSH level). The HRs and 2-sided 95% CI showed favorable outcomes for lenvatinib compared with placebo for PFS for all the subgroups.
- Four (1.5%) subjects treated with lenvatinib had a BOR of CR while no subjects in the placebo group had a CR, and 165 (63.2%) subjects had a PR compared with 2 (1.5%) subjects in the placebo group. The secondary endpoint, ORR based on the IIR assessments, was significantly higher with lenvatinib treatment. The ORR was 64.8% in the lenvatinib arm compared with 1.5% in the placebo arm. The odds ratio was 28.87, which was statistically significant (P<0.0001) in favor of lenvatinib. The median duration of objective response for the lenvatinib arm was not yet reached at the time of data cutoff. Among the responders, 75% had a duration of response of greater than 9.4 months, and the median time to the first objective response was 2.0 months for the lenvatinib group.
- Although OS was a secondary endpoint, the study was not designed to demonstrate a survival difference with the crossover design and limited statistical power. The analysis for OS included data from the placebo-treated subjects with confirmed disease progression who entered into the OOL Lenvatinib Treatment Period of the Extension Phase. At the data cutoff date, the median OS was not yet reached for either the lenvatinib arm or the placebo arm (including crossover subjects). When adjusted for the treatment crossover, using the prespecified RPSFT model, the HR was 0.62 (95% CI: 0.40, 1.00), showing a trend toward prolongation of OS with lenvatinib as compared with placebo. The difference in OS between the 2 treatment arms was marginally significant as determined using the resampling method (bootstrapping) (P=0.0510). The adjusted OS rates were numerically higher in the lenvatinib arm compared with the placebo crossover arm (6 months: 90.7% vs 85.3%, respectively; 12 months: 81.6% vs 70.0%, respectively; 18 months: 72.3% vs 63.0%, respectively). Using the unadjusted stratified Cox proportional hazard model, the HR was 0.73 (95% CI: 0.50, 1.07), showing a trend in favor of lenvatinib treatment for prolonged OS, as was observed with the adjusted model.

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics

The PK analyses are provided in an auxiliary report (CPMS-E7080-007R-v1), as are the results of the pharmacogenomic analyses (CPMS-E7080-007PHENO).

Safety

- The median duration of exposure was 13.8 months (range: 0 to 27 months) for lenvatinib and 3.9 months (range: 0 to 24 months) for placebo.
- Total exposure was 4 times longer for lenvatinib compared to placebo (260.9 subject-years for lenvatinib and 65.0 subject-years for placebo).
- The most common TEAEs (≥30%) of any grade with lenvatinib and placebo, respectively, were: hypertension (69.3% vs 14.5%), diarrhea (66.3% vs 16.8%), decreased appetite (53.3% vs 18.3%),

weight decreased (50.6% vs 14.5%), nausea (46.4% vs 25.2%), fatigue (42.1% vs 24.4%), headache (38.3% vs 11.5%), stomatitis (35.6% vs 6.9%), vomiting (35.2% vs 14.5%), palmar-plantar erythrodysesthesia (PPE) syndrome (32.2% vs 0.8%), proteinuria (32.2% vs 3.1%), and dysphonia (31.4% vs 5.3%). The TEAEs reported in the lenvatinib arm are consistent with those observed in the Phase 2 trials.

- Severe (Grade 3 or 4) TEAEs were reported more frequently in the lenvatinib arm (72.4% and 11.9%, respectively) than in the placebo arm (22.1% and 7.6%, respectively). The most frequently reported severe TEAEs (≥10%) in the lenvatinib arm were hypertension, weight decreased, and proteinuria.

- Serious AEs (including fatal and nonfatal) were reported more frequently in the lenvatinib arm (51.0%) than in the placebo arm (23.7%). The incidence of SAE episodes adjusted for treatment duration in the lenvatinib and placebo arms, respectively, were 1.05 and 0.83 episodes per subject-year. The most frequently reported SAEs were coded to the SOCs of Infections and Infestations and Nervous System disorders. Serious AEs appeared to be mainly due to comorbidities or underlying conditions. No novel pattern for SAEs was detected.

- AEs led to discontinuation of lenvatinib in 16.5% of subjects (the investigator specified AE as the primary cause of discontinuation in 14.2% of subjects in the lenvatinib arm). Most subjects tolerated lenvatinib when the protocol-specified algorithm of dose interruptions/reductions and concomitant medications was followed.

- AEs led to dose reduction or interruption of study drug in 89.3% of subjects treated with lenvatinib. The majority of AEs leading to study drug reduction or interruption were Grade 3 or lower, suggesting that subjects had their dose reduced or interrupted at the first occurrence of an AE, as specified in the protocol.

- The following categories of events were identified as clinically significant based on a detailed review of the safety data: hypertension, proteinuria, liver injury/failure, renal failure/impairment, arterial thromboembolic events, venous thromboembolic events, and posterior reversible encephalopathy and syndrome (PRES). All AEs in these categories occurred more frequently in the lenvatinib arm than the placebo arm. Although causality secondary to the administration of lenvatinib cannot be completely ruled out due to its anti-angiogenic effects, it would appear that other confounding factors may have contributed to many of these events.

- The most frequent Grade 3 or 4 laboratory abnormalities in the lenvatinib and placebo arms, respectively, were decreased lymphocyte count (10.0% vs 9.9%), hypocalcemia (8.4% vs 1.5%), and hypokalemia (6.1% vs 0.8%). Grade 4 hypocalcemia occurred in 10 (3.8%) lenvatinib-treated subjects and 0 placebo-treated subjects. Grade 4 hematology, liver, and renal abnormalities each occurred in no more than 1 subject in the lenvatinib arm.

- In the lenvatinib arm, weight loss and increased blood pressure (BP) occurred early during treatment, beginning on Cycle 1 Day 15. Weight loss continued throughout the treatment period, with the greatest weight loss occurring in the highest BMI category (≥30 kg/m^2) and minimal loss in the lowest BMI category (<18.5 kg/m^2). In the lenvatinib and placebo arms, respectively, the median change from baseline was -1.0 kg and 0.0 kg at Cycle 1 Day 15 and -5.1 kg and -1.0 kg at the end-of-treatment measurement. Blood pressure appeared to stabilize in later cycles, probably due to the introduction of antihypertensive medication, dose reduction, or both. There were no consistent changes over time in body weight or BP in the placebo arm.

- The ECG parameters showed no trends over time in either treatment arm. The percentage of subjects with a maximum QTcF >500 ms and a QTcF >60 ms increase from baseline was 2.7% and 9.2% in the lenvatinib arm and 0.8% and 3.1% in the placebo arm, respectively. All occurrences of maximum QTc >500 ms and >60 ms increases in QTcF from baseline in lenvatinib-treated subjects were single, isolated episodes. Results from the thorough QTc study (E7080-A001-002) demonstrated that

lenvatinib does not exert a clinically relevant effect on the QTc interval in healthy subjects.

- Treatment-emergent AEs of decreased ejection fraction were reported in 4.6% of subjects in the lenvatinib arm and 0.8% of subjects in the placebo group. Five of the 12 lenvatinib-treated subjects had potential confounding factors, eg, hypertension, diabetes mellitus, hyperlipidemia, or obesity. The majority of the events were mild dysfunction, moderate decrease in the ejection fraction was rare, and no SAEs were reported. Due to the presence of individual risk, the low rate of the TEAE of decreased ejection fraction observed, and the lack of findings in a previous echocardiographic study (E7080-G000-204), it is unclear that lenvatinib has any contribution to dysfunction.

Conclusions

Results from this study demonstrate that lenvatinib is effective in the treatment of RR-DTC and has an acceptable safety profile when treatment is initiated at 24 mg QD and adjusted by a dose-titration algorithm to manage toxicity.

Date of Report

5 June 2014