CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Division Director Summary Review

Date	February 11, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 206947
Applicant Name	Eisai Inc.
Date of Submission	August 14, 2014
PDUFA Goal Date	April 14, 2015
Proprietary Name / Established (USAN) Name	Lenvima/ lenvatinib
Dosage Forms / Strength	capsule for oral administration/ 4 mg and 10 mg
Proposed Indication(s)	"for the treatment of patients with progressive, radioiodine-refractory differentiated thyroid cancer"
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Deanne Varney
Medical Officer Review	Abhilasha Nair
Statistical Review	Janet (Xiaoping) Jiang
Pharmacology Toxicology Review	Emily Fox
CMC Review	Gaetan Ladouceur and Amit K. Mitra
Biopharmaceutics Review	Okpo Eradiri
Clinical Pharmacology Review	Jun Yan, Anshu Marathe, Ping Zhao, Robert Schuck
QT-IRT Review	Jiang Liu
OPDP	Nick Senior
Patient Labeling Team Review	Nathan Caulk
OSI	Lauren Iacono-Conors
CDTL Review	Steven Lemery
OSE/DMEPA Review	Otto Townsend
OSE/DRISK Review	Carolyn Yancey
DPMH Consult	Miriam Dinatale

OND=Office of New Drugs
CMC=Chemistry, Manufacturing, and Controls
QT-IRT=QT Interdisciplinary Review Team
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DPMH=Division of Pediatric and Maternal Health

Division Directory Summary Review

1. Introduction

LENVIMA (lenvatinib mesylate), 4 mg and 10mg capsules, was approved for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC). This approval is based on the demonstration of clinically important and statistically robust improvement in progression-free survival demonstrated in a single adequate and well-controlled clinical trial. The risks of lenvatinib are acceptable in this patient population with a serious and life-threatening disease and the overall risk:benefit assessment is acceptable.

Lenvatinib inhibits multiple receptor tyrosine kinases, including VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet derived growth factor (PDGF) receptor PDGFRα, KIT, and RET.

The major efficacy trial, Study E7080-G000-303 (SELECT), was a multicenter, randomized (2:1), double-blind, placebo-controlled trial conducted in 392 patients with locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within 12 months prior to randomization, confirmed by independent radiologic review. Patients were randomized to receive LENVIMA 24 mg once daily (n=261) or placebo (n=131) until disease progression. Randomization was stratified by geographic region, prior VEGF/VEGFR-targeted therapy, and age.

A statistically significant prolongation in PFS was demonstrated in LENVIMA-treated patients compared to those receiving placebo [HR 0.21 (0.16, 0.28), $p<0.001$], with a difference in median PFS of 14.7 months (median PFS 18.3 months for lenvatinib and 2.6 months for placebo). In addition, the objective response rate was significantly higher in the lenvatinib arm (65% vs. 2%, $p < 0.001$). There were too few events to conduct a formal analysis of survival, however an unplanned interim analysis conducted at FDA's request did not suggest an impairment of survival for patients receiving lenvatinib.

Safety was evaluated in 362 patients receiving at least one dose of study-specific treatment; this included 261 patients who received lenvatinib and 131 who received placebo. Lenvatinib was poorly tolerated at the starting dose of 24 mg daily, with 68% of patients requiring dose reduction and 18% of patients discontinuing lenvatinib for adverse reactions as compared to 5% requiring dose reduction and 5% discontinuing placebo for adverse reactions. The most common adverse reactions resulting in lenvatinib dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions resulting in discontinuation of lenvatinib were hypertension (1%) and asthenia (1%).

Adverse reactions reflected the spectrum of kinase inhibition by lenvatinib, including adverse reactions likely resulting from inhibition of VEGFR as well as adverse reactions from inhibition of other pathways (e.g., fatigue, gastrointestinal symptoms, and cutaneous toxicity). The most common adverse reactions of lenvatinib were hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%),

nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar erythrodysesthesia (PPE) syndrome (32%), abdominal pain (31%), and dysphonia (31%). The most common serious adverse reactions of lenvatinib were pneumonia (4%), hypertension (3%), and dehydration (3%).

The review team members unanimously recommended approval. The treatment effects on PFS are clinically important and robust and outweigh the risks of lenvatinib toxicity in this patient population. The adverse reaction profile of lenvatinib was similar in spectrum to other "promiscuous" tyrosine kinase inhibitors. Given the serious and life-threatening nature of differentiated thyroid cancer which is refractory to radioiodine, with an estimated 10-year survival of 10%, the risks of treatment are acceptable in this population.

The major issue raised in this application was the appropriate dose and whether efficacy could be preserved at a lower, less toxic dose. This is discussed in greater detail in Section 8 of this review. Given the poor tolerability of the approved dose, FDA required a post-marketing study under 505(o) to further evaluate the serious risks of lenvatinib at starting doses of 20 mg and at 14 mg, to further assess the adverse reaction profile and exposure-toxicity relationship lenvatinib. Since this study will be conducted in patients with RAI-refractory DTC, preliminary evidence of activity at these alternate starting doses will also be collected.

2. Background

Background regarding differentiation thyroid cancer and available therapies

Radioiodine-refractory differentiated thyroid cancer is a serious and life-threatening disease, with an estimated 10-year survival rate of approximately 10%. There are two drugs approved for this population: doxorubicin and sorafenib.

- Doxorubicin was approved in mid-1970's for the treatment of nine cancer types, including thyroid cancer.[1] The basis for approval for the treatment of thyroid cancer is objective tumor shrinkage (response rate), with literature at the time of the initial approval citing a 30% response rate (14/46) in patients with advanced refractory, metastatic thyroid carcinoma from single-arm trials. There is no evidence from published literature that doxorubicin improves overall survival or progression-free survival.

- Sorafenib received regular approval in 2013 for the treatment of radiation-refractory, progressive, differentiated thyroid cancer, based on the results of randomized, placebo-controlled trial (DECISION) enrolling 471 patients. The trial demonstrated a statistically significant and clinically important improvement in PFS [hazard ratio (HR) 0.59 (95% confidence intervals (CI): 0.45, 0.76); p <0.001, two-sided stratified log-rank test] with median progression-free survival times of 10.8 months in the sorafenib arm and 5.8 months in the placebo arm. The overall response rate, consisting of partial responses, was higher

[1] Adriamycin - A Review. Carter SK; JNCI 1975 Dec;55(6):1265-74.

for the sorafenib arm compared with placebo (12.2% vs. 0.5%). The median duration of response was 10.2 months in sorafenib arm and 20 months for the single response observed in the placebo arm.

Pre-Submission History

March 31, 2005: IND (b) (4) submitted for development of lenvatinib (b) (4)

January 12, 2011: EOP2 meeting to discuss results of trials Study E7080-A001-102 (Phase 1) and Study E7080-G000-201, which was conducted in patients with thyroid cancer, and to discuss the adequacy of the ongoing trial, Study E7080-G000-303, as the single efficacy trial intended to support a proposed NDA for the treatment of radioactive iodine-refractory differentiated thyroid cancer. As proposed at this meeting, Study 303 was designed to demonstrate an improvement in median progression-free survival (PFS) with a hazard ratio of 0.57 (14 vs. 8 months) at a two-sided alpha of 0.01 (stratified log rank test). FDA agreed that a primary endpoint of PFS in a study that was well designed and conducted was acceptable provided that the trial demonstrated a robust, statistically persuasive, and clinically meaningful improvement in PFS with internal consistency of secondary endpoints and a favorable risk-benefit profile. FDA provided additional advice to Eisai concerning the statistical analysis plan for the trial.

March 3, 2011: Study E7080-G000-303 was submitted to IND (b) (4)

November 2, 2011: IND 113656 submitted to the Division of Oncology Drug Products 2 (DOP2) for the clinical development program of lenvatinib for treatment of radioiodine-refractory, differentiated thyroid cancer.

July 17, 2013: FDA issued a letter granting conditional approval for the proposed proprietary name, LENVIMA.

March 25, 2014: pre-NDA meeting was held and the following agreements were reached:

- The summary data appeared sufficient to support filing of the planned NDA and agreement was reached on the content of a complete application;
- Studies supporting the safety database would need to isolate the effects of lenvatinib, therefore, safety data from single arm studies of lenvatinib given in combination with additional anti-cancer agents would not be used to characterize the toxicity profile event if provided in the NDA.
- FDA raised concern that the appropriate dose of lenvatinib had not been established for this patient population; Eisai agreed to identify ongoing or post-marketing studies that would be used to determine whether a lower dose or alternative dosing regimen may result in comparable efficacy with less toxicity in this patient population.

Submission History

August 14, 2014: NDA received. The NDA was granted priority review status based on the unmet medical need in the subgroup of patients who had received prior anti-VEGF/VEGFR therapy. The DECISION trial supporting expanded labeling claims for sorafenib for this patient population excluded patients with prior anti-cancer treatment with tyrosine kinase inhibitors, monoclonal antibodies (licensed or investigational) that target VEGF or VEGF receptors or other targeted agents. Only 3% of patients in the DECISION trial had received prior systemic anti-cancer therapy.

In contrast, the SELECT trial allowed both prior chemotherapy and prior anti-VEGFR directed therapy. In addition, prior anti-VEGFR therapy was one of three stratification variables (in addition to region and age). Approximately 10% of patients in both arms received prior chemotherapy. As described in the clinical study report, there were 66 (25.3%) patients among the 261 randomized to lenvatinib and 27 (20.5%) among the 131 randomized to placebo who had received anti-VEGF/VEGFR therapy. The most common prior anti-VEGF therapy was sorafenib [19.5% (levantinib) and 16% (placebo)], followed by sunitinib (1.9% and 2.3%), pazopanib (1.1% and 1.5%), and "other" (2.7% and 0.8%).

The statistical reviewer confirmed the findings reported by Eisai for the stratum who had received prior anti-VEGF/VEGFR therapy. In this subgroup, the treatment effect of lenvatinib on PFS was similar among those who did [HR 0.22 (95% CI 0.12, 0.41)] and those who did not [HR 0.20 (95% CI 0.14, 0.27)] receive prior anti-VEGF therapy. In addition, the objective response rate among patients who received prior anti-VEGF was similar to the overall population.

November 4, 2014: teleconference to obtain clarification on drug product manufacturing, testing, and packaging sites.

November 4, 2014: Mid-cycle meeting held

November 19, 2014: Post mid-cycle communication held with Eisai.

November 25, 2014: teleconference to discuss potential risks of medication errors for the proposed proprietary name, Lenvima.

February 4, 2015: Late cycle meeting was held.

3. CMC/Biopharmaceutics

I concur with the conclusions reached by the drug product, drug substance, quality microbiology, and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. There are no outstanding sterility issues. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months when stored at 25 °C There are no outstanding issues that preclude approval.

As noted in the quality reviews, lenvatinib is manufactured as a mesylate salt. (b) (4) . It is not hygroscopic and has a very low solubility in aqueous solutions. It will be marked as immediate release oral capsules in strengths of 4-mg and 10-mg.

The Quality Review Team requested, and Eisai agreed, to set a limit (b) (4) and submit a method for measuring (b) (4) with validation of this new method as a post marketing commitment (PMC).

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

The NDA contained the reports of in vivo (tumor xenograft) and in vitro studies supporting the anti-angiogenic and tumor growth inhibition of lenvatinib. In addition, the NDA contained reports of repeat-dose toxicology studies with daily dosing for up to 26 and 39 weeks in rats and monkeys, respectively, safety pharmacology studies, and embryofetal development studies.

As noted by in the reviews, metabolism of lenvatinib appeared similar between species and unchanged parent was the major product in plasma. Elimination was primarily through the fecal route in animals and humans. Lenvatinib was widely distributed in animal tissues with high levels of the drug observed in the GI tract, liver, kidney, and aorta all target organs identified clinically. The major target organs identified in general toxicology studies conducted in rats, monkeys, and dogs included the gastrointestinal tract, kidney, liver, pancreas, bone marrow, growth plates, teeth, secondary lymphoid organs, adrenal gland, and pituitary.

No significant behavioral or physiological changes were observed following a single dose of lenvatinib in safety pharmacology studies. While transient elevations in blood pressure were noted following a single dose of lenvatinib in monkeys and there was no evidence of effects on cardiac electrophysiology based on ECG monitoring in repeat-dose studies.

In embryofetal development studies conducted in both rats and rabbits, lenvatinib was embryotoxic, fetotoxic, and teratogenic at exposures below that achieved in humans receiving lenvatinib at a dose of 24 mg daily. Lenvatinib was detected in milk from lactating rats treated with the drug at levels approximately two-fold higher than plasma concentrations.

Concerns raised regarding the potential for neurological development in juvenile animals by the nonclinical pharmacology/toxicology reviewer were resolved during the review. The findings of impairment of maze navigation were attributed to fatigue (also seen at a high incidence in clinical studies) rather than neurologic impairment.

With regard to determination of the duration of contraception, the recommendation in labeling is based on the half-life of the product, which is relatively short, and on evidence of fetal harm

in the embryofetal development studies rather than general toxicology studies, resulting in a recommendation to continue contraception for 2 weeks (b) (4) after the last dose of lenvatinib.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The data provided in the NDA provided adequate support for dosing directions with the exception of the recommended starting dose of 24 mg daily. The major efficacy study indicated that this dose was poorly tolerated when chronically administered. See further discussion under Section 8 of this review.

The clinical pharmacology reviewers evaluated pharmacokinetic data from 16 studies including several dose-finding, safety and tolerability studies in patients with various cancers, renal and hepatic impairment studies, a food effect study, a formulation (capsule vs. tablet) bridging study, drug interaction studies, and a thorough QT (TQT) study conducted in healthy volunteers who received at a single 32 mg dose. A population PK (PopPK) analysis was performed using pooled data collected from studies in healthy subjects, dose-finding, safety and tolerability studies, and Study 303.

Based on these data, lenvatinib was shown to have rapid absorption with maximal concentrations (C_{max}) ranging from 1 to 4 hours after oral administration and a terminal elimination half-life of 28 hours. The bioavailability of lenvatinib was not altered when taken after a high-fat meal as compared to the fasted state, although the median C_{max} was prolonged from 2 to 4 hours. Exposure to lenvatinib (C_{max} and AUC) increased proportionally over the dose range of 3.2 to 32 mg. In vitro, lenvatinib is predominantly bound to human plasma proteins (98% to 99% bound) and measurement of free lenvatinib is variable, thus the pharmacokinetic reviewers relied on total lenvatinib concentrations in assessing its pharmacokinetic properties.

Based on popPK analyses, there were no clinically important pharmacokinetic interactions between lenvatinib and body weight, gender, race, age, or tumor type. Although the solubility of lenvatinib is pH-dependent, there were no conclusive effects of gastric pH modifying agents (proton-pump inhibitors, H_2 blockers, antacids) on the pharmacokinetics of lenvatinib.

Based on organ impairment studies, increased total lenvatinib exposures ($AUC_{0\text{-inf, total}}$) of 119%, 107%, and 180% were observed in patients with mild, moderate, or severe hepatic impairment, respectively, as compared to those with no impairment.

Although lenvatinib is metabolized by CYP3A (and by aldehyde oxidase as well as non-enzymatic pathways), there was no clinically significant effects on lenvatinib exposure by a strong CYP3A4 inhibitor and dose adjustments of lenvatinib are not required when it is administered in conjunction with inhibitors of CYP3A, P-gp, and BCRP or with inducers of CYP3A and P-gp.

No clinically significant increase in total lenvatinib exposure ($AUC_{0\text{-inf, total}}$) was seen in subjects with severe renal impairment. However, since 90% of the lenvatinib-treated patients in Study 303 in the treatment arm of the registration trial underwent dose reduction and/or dose interruption and patients with severe renal impairment are vulnerable to renal toxicities including renal failure, dose adjustment is recommended in patients with severe renal impairment.

Although there was no evidence of an exposure-response (PFS) relationship in Study 303, this may have been confounded by the fact that 90% of patients receiving lenvatinib underwent a dose modification (dose reduction or dose delay).

Conflicting data on the effects of lenvatinib on cardiac electrophysiology were provided in the thorough QT study evaluating the effect of a single 32 mg dose of lenvatinib on the QT/QTc interval in 52 healthy individuals and the results of serial ECG monitoring in Study 303. The thorough QT study did not demonstrate prolongation of the QT/QTc interval, whereas prolongation of QTc was documented in 8.8% of lenvatinib-treated patients with Grade ≥3 QTc prolongation in 1.5% of lenvatinib-treated patients.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The efficacy data supporting this approval is derived primarily from a single, randomized (2:1), placebo-controlled, multicenter trial. Based on FDA's inspection of selected clinical sites participating in this trial, the data in this application are deemed reliable and review of the financial disclosure forms did not identify evidence of bias in the results from financial conflicts of interest. The study design and conduct was adequate and well-controlled, with auditing of the primary and key secondary efficacy results by an independent review committee that was masked to treatment assignment.

The development program for lenvatinib for this indication included three key studies: two trials in patients with thyroid cancer (Studies 201 and 208), and the major efficacy trial, E7080-G000-303. The 208 trial, being conducted in Japan, was ongoing and did not provide supportive efficacy data for this NDA.

Study 201 (E7080-G000- 201) was an open-label, parallel cohort study that evaluated the antitumor activity, pharmacokinetics (PK), and safety of lenvatinib in patients with medullary thyroid cancer (MTC) and in patients with radioiodine-refractory DTC. The primary objectives of the study were to determine the objective response rate (ORR) based on the modified Response Evaluation Criteria in Solid Tumors (RECIST) as assessed by the independent radiologic review, and to determine the PK profile and the PK/PD relationships of lenvatinib. A total of 117 patients (58 with DTC and 59 with MTC) were treated with lenvatinib; all but

two patients were treated at a dose of 24 mg daily. Among patients with DTC, the ORR was 50%; the ORR was 59% in patients who had received prior VEGF-targeted therapy (n=17) and 46% in patients who had not received prior VEGFR-targeted therapy (n=41). The median duration of response was 12.7 months.

Study Design – Study 303

Title: Study E7080-G000-303 "SELECT: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in 131I-Refractory Differentiated Thyroid Cancer"

Treatment plan: Patients were randomized to receive LENVIMA 24 mg once daily or matching placebo until disease progression. Randomization was stratified by geographic region (Europe vs. North America vs. other), age (≤ 65 years vs. >65 years), and prior VEGF/VEGFR-directed therapy (0 vs. 1). Patients in the placebo arm could receive lenvatinib following independent review confirmation of disease progression

Key eligibility criteria were: 1) locally recurrent or metastatic radioactive iodine-refractory differentiated thyroid cancer and 20 radiographic evidence of disease progression within 12 months prior to randomization as confirmed by independent radiologic review prior to study entry. Radioactive iodine (RAI)-refractory was defined as

- one or more measurable lesions with no iodine uptake on RAI scan,
- iodine uptake with progression within 12 months of RAI therapy, or
- cumulative RAI activity of >600 mCi (22 GBq) with the last dose administered at least 6 months prior to study entry.

The primary objective progression-free survival (PFS) and key secondary objectives were overall response rate (ORR) and overall survival (OS).

Analysis plan: The primary analysis of PFS was to be a log-rank test stratified by region (Europe, North America, Other), age group (≤65, >65 years), and prior VEGF/VEGFR therapy (0, 1) at two-sided significance level of 0.01, conducted in the intent-to-treat (ITT) population, defined as all randomized patients. The sample size of 360 patients was based on the following assumptions: 214 PFS events were needed to detect a significant improvement in PFS with 90% power at a 2-sided alpha level of 0.01, assuming that the true PFS hazard ratio was 0.57 and that the median PFS was 8 months in the placebo arm and 14 months in the lenvatinib arm. The secondary endpoint OS would be compared using a stratified log-rank test (variables used for randomization) at two-sided alpha of 0.05. The overall family-wise error rate at level $\alpha = 0.05$, would be controlled using a sequential testing procedure where ORR would be tested first at the 0.05 level and only if comparison of ORR was significant, would OS be tested, at the 0.05 level.

Results

The trial was conducted at 117 study sites in Europe, North America, Asia, and Latin America between July 26, 2011 and the data cutoff date of Nov 15, 2013, for the analyses of PFS and ORR. There were 392 patient randomized, 261 to lenvatinib and 131 to placebo. Baseline

demographic and prognostic factors were similar between arms, with the exception of a higher proportion of males in the placebo arm. The study population characteristics were 51% male, median age of 63 years with 40% older than 65 years, 79% White, 54% with an ECOG performance status of 0, and 24% had received VEGF/VEGFR-targeted therapy. The majority (99%) of patients had metastatic disease; sites of metastatic disease were lung (89%), lymph nodes (52%), bone (39%), liver (18%), and brain (4%). The histological diagnoses were papillary thyroid cancer (66%) and follicular thyroid cancer (34%); of those with follicular histology, 44% had Hürthle cell and 11% had clear cell subtypes. There were 67% of patients randomized to lenvatinib who did not demonstrate iodine uptake on any radioiodine scan compared to 77% in the placebo arm. Additionally, 59% of patients on the LENVIMA arm and 61% of patients on placebo arm progressed, according to RECIST 1.1, within 12 months of prior ^{131}I therapy. A minority (19.2%) of patients randomized to lenvatinib and 17.6% randomized to placebo arm received prior cumulative activity of >600 mCi or 22 gigabecquerels (GBq) ^{131}I, with the last dose administered at least 6 months prior to study entry. The median cumulative RAI activity administered prior to study entry was 350 mCi (12.95 GBq).

The primary reason for treatment discontinuation in the placebo arm was disease progression, whereas the primary reason for treatment discontinuation in the lenvatinib arm was adverse reaction (14%) with an additional 3% of patients discontinuing treatment for "subject choice" or "withdrawal of consent". Upon confirmation of progression, 109 (83%) patients randomly assigned to placebo received lenvatinib following IRC-documented disease progression.

The table and figure below, abstracted from the product labeling, summarize the results of the final analyses of PFS and ORR. The effects on PFS were robust as determined by the test statistic and multiple sensitivity analyses conducted by the statistical reviewer. In addition, the effects on PFS were consistent in subgroups based on age, gender, race/ethnicity, geographic region, histologic subtype, ECOG performance status, and prior exposure to anti-VEGF/VEGFR therapy. An unplanned analysis of overall survival was conducted at FDA's request as part of the risk:benefit assessment. This analysis did not suggest detrimental effects on survival for patients randomized to lenvatinib.

Efficacy Results for Study 303

	LENVIMA N=261	Placebo N=131
Progression-free Survival[a]		
Number of events (%)	107 (41)	113 (86)
Progressive disease	93 (36)	109 (83)
Death	14 (5)	4 (3)
Median PFS in months (95% CI)	18.3 (15.1, NE)	3.6 (2.2, 3.7)
Hazard ratio (95% CI)[b]	0.21 (0.16, 0.28)	
P-value[c]	<0.001	
Objective Response Rate[a]		
Objective response rate	65%	2%
(95% CI)	(59%, 71%)	(0%, 4%)
Complete response	2%	0%
Partial response	63%	2%
P-value[d]	<0.001	
Overall Survival[e]		
Number of deaths (%)	71 (27)	47 (36)
Median OS in months (95% CI)	NE (22.1, NE)	NE (20.3, NE)
Hazard ratio (95% CI)[b]	0.73 (0.50, 1.07)	
P-value[b]	0.10	

[a] Independent radiologic review

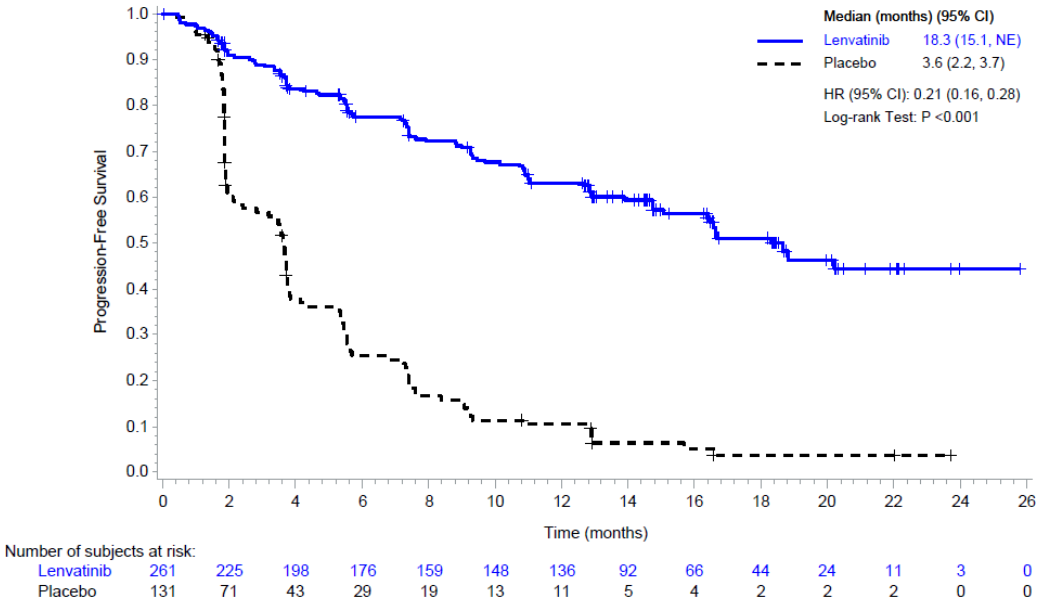
[b] Estimated with Cox proportional hazard model stratified by region (Europe vs North America vs other), age group (≤65 year vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)

[c] Log-rank test stratified by region (Europe vs North America vs other), age group (≤65 years vs >65 years), and previous VEGF/VEGFR-targeted therapy (0 vs 1)

[d] Cochran-Mantel-Haenszel chi-square test

[e] NE = Not estimable

Progression-Free Survival Curves for Study 303



8. Safety

Size of the database

Safety data obtained in 1108 patients with advanced solid tumors who received LENVIMA as a single agent across multiple clinical studies; the size of the safety database was adequate to identify serious adverse drug reactions occurring at an incidence of 0.3%. The median age was 60 years (range 21-89 years). The dose range was 0.2 mg to 32 mg. The median duration of exposure in the entire population was 5.5 months.

The incidence of common adverse reactions were based on data obtained in Study 303, in which 261 patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC) received at least one dose of lenvatinib and 131 patients received at least on dose of placebo. The median duration of lenvatinib treatment was 16 and the median duration of placebo administration was 3.9 months. Across this safety population of 392 patients with RAI-refractory DTC, the median age was 64 years, 52% were women, 80% were White, 18% were Asian, and 2% were Black. At baseline, more than 85% of patients had adequate suppression of thyroid function (TSH $\leq$ 0.5microIU/mL).

The most common adverse reactions of lenvatinib hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar erythrodysesthesia (PPE) syndrome (32%), abdominal pain (31%), and dysphonia (31%). The most common serious adverse reactions of lenvatinib were pneumonia (4%), hypertension (3%), and dehydration (3%).

Lenvatinib was poorly tolerated at the starting dose of 24 mg daily, with 68% of patients requiring dose reduction and 18% of patients discontinuing lenvatinib for adverse reactions as compared to 5% requiring dose reduction and 5% discontinuing placebo for adverse reactions. Based on concerns raised by the Data Safety and Monitoring Committee (DMC) that excessive toxicity was experienced by patients receiving the 24 mg daily dose, the protocol was amended to lower the lenvatinib dose received by patients from the placebo arm who were allowed to receive lenvatinib following documentation of disease progression to 20 mg orally, once daily.

The most common adverse reactions resulting in lenvatinib dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions resulting in discontinuation of lenvatinib were hypertension (1%) and asthenia (1%).

Major safety concern

The major safety concerns are described in the Warnings section of the agreed-upon product labeling and included:

- The increased risks of severe or life-threatening hypertension (44% vs. 4% Grade 3, <1% vs. none for Grade 4);

- An increased risk of cardiac dysfunction (7% vs. 2% overall incidence and 2% incidence vs. none of ≥ Grade 3 cardiac dysfunction) consisting of decreased ventricular function or heart failure/pulmonary edema;
- An increased risk of arterial thrombolic events (5% vs. 2% overall incidence and 3% vs. 1% incidence ≥ Grade 3);
- The risk of hepatic failure and acute hepatitis, reported in three patients and in one patient, respectively, across entire safety database of 1108 lenvatinib-treated patients; 4% incidence of Grade ≥3 ALT and 5% incidence of ≥ Grade 3 AST elevations in Study 303;
- An increased risk of proteinuria (34% vs. 3% overall incidence and 11% vs. none ≥ Grade 3 incidence);
- An increased risk of renal impairment (14% vs. 2% overall incidence and 3% vs. 1% ≥ Grade 3 incidence);
- An increased risk of gastrointestinal perforation or fistula (2% vs. 0.8%);
- An increased risk of QT/QTc interval prolongation (9% vs. 2% overall incidence and 2% vs. none for ≥ Grade 3 QT prolongation);
- An increased risk of ≥ Grade 3 hypocalcemia (9% vs. 2%);
- The risk of reversible posterior leukoencephalopathy syndrome (RPLS) with three cases reported across the safety database of 1108 patients;
- An increased risk of Grade 1 to 2 hemorrhage (35% vs. 18% overall incidence), where the most frequently reported hemorrhagic event in the lenvatinib arm was epistaxis (11% Grade 1and 1% Grade 2); and
- An increased risk of loss of TSH suppression, with elevation of TSH levels post-baseline in 57% of lenvatinib -treated patients as compared with 14% of those in the placebo arm.

REMS

I concur with the recommendations of the review team and DRISK consultant that a Risk Evaluation and Mitigation Strategy (REMS) is not required to ensure safe and effective use and that adequate directions for safe use can be conveyed in product labeling. Management of serious adverse reactions of the lenvatinib is well known to oncologists who administer other anti-VEGF-therapy (hypertension, proteinuria, viscus perforation, hemorrhage, and wound healing) and anti-EGFR-directed (cutaneous toxicity) and traditional cytotoxic chemotherapy (gastrointestinal toxicity, including diarrhea, nausea, vomiting, abdominal pain).

PMRs and PMCs

As discussed earlier in this section, the starting dose of lenvatinib (24 mg daily) employed in Study 303 was poorly tolerated; 68% of patients requiring dose reduction and 18% of patients discontinuing lenvatinib for adverse reactions. The development program did not provide sufficient dose ranging to determine the optimal dose of lenvatinib, however it was also unclear whether lower doses would be better tolerated or similarly effective. In order to further explore the exposure-toxicity relationship, a post-marketing requirement (reproduced below) has been required. Since this trial will enroll patients with RAI-refractory DTC,

preliminary information on anti-tumor activity (overall response rate) for the 20 mg and 14 mg doses will be available to determine if additional trials should be conducted for dose optimization.

Conduct a clinical trial to evaluate the incidence of serious and severe (i.e. ≥ Grade 3) adverse reactions of an oral starting dose of 20 mg or of 14 mg daily compared to the 24 mg starting dose, with a comparable objective response rate. Safety assessments will include evaluations for all severe or life-threatening (≥ Grade 3) and serious adverse reactions and should also include assessments of all adverse reactions.

9. Advisory Committee Meeting

This application for lenvatinib, a new molecular entity, was not referred to the Oncologic Drugs Advisory Committee because the safety profile is acceptable for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, the clinical trial design of Study 303 was acceptable to demonstrate clinical benefit; the application did not raise significant safety or efficacy issues that were unexpected for an inhibitor of multiple tyrosine kinases in the EGFR superfamily; the application did not raise significant public health questions on the role of the drug in the treatment of radioiodine-refractory, differentiated thyroid cancer; and there were no controversial issues identified during the review of this application that would benefit from advisory committee discussion.

10. Pediatrics

Eisai was granted Orphan Drug Designation on December 27, 2012 for lenvatinib for the "treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer." Therefore, lenvatinib is exempt from the requirements of the Pediatric Research Equity Act (PREA) for the proposed indication, which is a subset of the broader indication cited in FDA's letter granting Orphan Drug Designation.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: Although initial concerns regarding look-alike names were raised, the risks of medication errors were considered to be low based on differences in route of administration, dosing, patient population, and pharmacy distribution (lenvatinib

will be distributed only to specialty pharmacies). DMEPA and the clinical review staff agreed that the proposed proprietary name of Lenvima was acceptable.

- Physician labeling
  - Boxed Warning: None proposed by Eisai; FDA did not require a Boxed Warning for sorafenib, which has similar a serious adverse reaction profile.
  - Indications and Usage: Added "locally recurrent or metastatic" to the indication statement
  - Dosage and Administration: edited for brevity and clarity; removed statement [redacted (b) (4)]" as there are no pharmacokinetic or other data supporting this restriction; moved recommended dosing information for patients with renal or hepatic impairment up to section 2.1;
  - Dosage Forms and Strengths: removed statement "[redacted (b) (4)]"
  - Contraindications: no modifications from proposed labeling
  - Warnings and Precautions: Reordered warnings based on likelihood that it would affect decision to prescribe lenvatinib (e.g., cardiac dysfunction moved up above proteinuria); added new subsections on hypocalcemia and impairment of TSH suppression (consistent with sorafenib labeling); retitle subsection [redacted (b) (4)] to embryofetal toxicity (to better describe risk); added information on actions to be taken to mitigate toxicity (e.g., withhold lenvatinib, increased monitoring).
  - Adverse Reactions: Included description of the demographic and disease characteristics of the safety population; re-ordered information in table based on descending order of incidence based on organ system; removed uninformative terms ([redacted (b) (4)]) and described incidence of oral pain and rash using composite terms; reported incidence of hypothyroidism based on elevated TSH rather than limited to clinical reports of the adverse event term "hypothyroidism", provided information on clinically significant events occurring at a low incidence in text rather than tabular format.
  - Drug Interactions: extensively edited for brevity
  - Use in Specific Populations: Labeling subsections for pregnant women, nursing mothers, males and females of reproductive potential and pediatric patients were revised in accordance with recommendations by the DPMH and the non-clinical pharmacology/toxicology reviewers and placed in the format of the draft Pregnancy and Lactation Labeling Rule (PLLR).
  - Description: Added "The dissociation constant (pKa value) of lenvatinib mesylate is 5.05 at 25°C. The partition coefficient (log P value) is 3.30"; edited solubility characteristics to essential information for prescribers/pharmacists.
  - Overdosage: Edited for accuracy ([redacted (b) (4)]) and added statement "Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable"
  - Clinical Pharmacology: Added "Lenvatinib also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions" to section 12.1 prior to description of

inhibition of specific receptor tyrosine kinases (RTKs); Added information on QT prolongation observed in Study 303 to the Cardiac Electrophysiology (12.2) subsection: Section 12.3 extensively edited for brevity and essential information; data on total lenvatinib emphasized over "free lenvatinib" for the reasons described in Section 5 of this summary review.

- Nonclinical Pharmacology/Toxicology: Added information suggesting impairment of fertility based on general toxicology studies since dedicated fertility studies were not conducted.
- Clinical Studies: Revised to include additional details regarding study design and characteristics of study population; removed statements (b) (4)
- How Supplied/Storage: Corrected information on NDC numbers for blister cards and cartons containing blister card; edited for brevity and essential information.
- Patient Counseling: edited for format in accordance with recently published FDA Guidance on this section of product labeling: added new subsections corresponding to individual subsections in Warnings and Precautions, where appropriate.

- Carton and immediate container labels: Agreement was reached on final carton and immediate container labeling; revisions included an updated NDC number and formatting in accordance with current regulations and FDA policy.

- Patient labeling/Medication guide: A medication guide was not required to ensure safe and effective use of lenvatinib. Eisai provided a patient package insert, which was revised for consistency with the final, agreed-upon physician package insert and in accordance with current labeling policy for patient labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of the review team and also recommend approval of this NDA.

- Risk Benefit Assessment

  I recommend approval for this new molecular entity, based on the results of Study 303, which demonstrated a clinically meaningful and statistically robust improvement in progression-free survival, supported by objective response rate of 65% in the major efficacy trial, which provides direct evidence of clinical benefit in this patient population whose expected 10-year survival is 10%. The risk:benefit assessment is favorable as the adverse reaction profile is similar to that observed with sorafenib, another drug approved for this indication, and medical oncologists are familiar with the identification and management of these adverse reactions.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  I concur with the recommendations of the review team and DRISK consultant that a Risk Evaluation and Mitigation Strategy (REMS) is not required to ensure safe and effective use and that adequate directions for safe use can be conveyed in product labeling.

- Recommendation for other Postmarketing Requirements and Commitments

  The clinical and clinical pharmacology review teams noted the poor tolerability of the 24 mg starting dose employed in the Study 303. However, prior to exploring the efficacy of lower doses, additional information would be needed to establish the adverse reaction profile and tolerability of lower doses, specifically 20 mg and 14 mg, which were employed in patients unable to tolerate the 24 mg dose. Therefore, FDA required that a post-marketing trial be conducted under 505(o), as follows:

  - Conduct a clinical trial to evaluate the incidence of serious and severe (i.e., ≥ Grade 3) adverse reactions of an oral starting dose of 20 mg or of 14 mg daily compared to the 24 mg starting dose, with a comparable objective response rate. Safety assessments will include evaluations for all severe or life-threatening (≥ Grade 3) and serious adverse reactions and should also include assessments of all adverse reactions.

  In addition, a post-marketing commitment was requested by the chemistry reviewer to develop and provided data supporting an alternative test for (b) (4).

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/s/

PATRICIA KEEGAN
02/12/2015