

FDA Approval Summary: Lenvatinib for Progressive, Radio-iodine-Refractory Differentiated Thyroid Cancer

Abhilasha Nair¹, Steven J. Lemery¹, Jun Yang², Anshu Marathe², Liang Zhao², Hong Zhao², Xiaoping Jiang³, Kun He³, Gaetan Ladouceur⁴, Amit K. Mitra⁴, Liang Zhou⁴, Emily Fox¹, Stephanie Aungst¹, Whitney Helms¹, Patricia Keegan¹, and Richard Pazdur¹

Abstract

The FDA approved lenvatinib (Lenvima, Eisai Inc.) for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory (RAI-refractory) differentiated thyroid cancer (DTC). In an international, multicenter, double-blinded, placebo-controlled trial (E7080-G000-303), 392 patients with locally recurrent or metastatic RAI-refractory DTC and radiographic evidence of disease progression within 12 months prior to randomization were randomly allocated (2:1) to receive either lenvatinib 24 mg orally per day ($n = 261$) or matching placebo ($n = 131$) with the option for patients on the placebo arm to receive lenvatinib following independent radiologic confirmation of disease progression. A statistically significant prolongation of progression-free survival (PFS) as determined by independent radiology review was demonstrated

[HR, 0.21; 95% confidence interval (CI), 0.16–0.28; $P < 0.001$, stratified log-rank test], with an estimated median PFS of 18.3 months (95% CI, 15.1, NR) in the lenvatinib arm and 3.6 months (95% CI, 2.2–3.7) in the placebo arm. The most common adverse reactions, in order of decreasing frequency, observed in the lenvatinib-treated patients were hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, decreased weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia. Adverse reactions led to dose reductions in 68% of patients receiving lenvatinib at the 24 mg dose and 18% of patients discontinued lenvatinib for adverse reactions leading to residual uncertainty regarding the optimal dose of lenvatinib. *Clin Cancer Res*; 21(23); 5205–8. ©2015 AACR.

Introduction

Based on Surveillance and Epidemiology and End Results (SEER) data, an estimated 62,980 new cases of thyroid cancer and an estimated 1,890 deaths due to thyroid cancer were reported in 2014 (1). Thyroid cancer occurs more frequently among people aged 45 to 54 and is more common in women than men and among those with a family history of thyroid disease (1). Localized thyroid cancer has a 5-year survival rate of 99.9% which decreases to 54.1% for patients diagnosed with distant metastases (1).

The prognosis is excellent for most patients with early stage differentiated thyroid cancer (DTC) who undergo surgical treatment followed by radioactive iodine (RAI) suppression; however, about 5% of patients develop RAI-refractory DTC which is generally not responsive to conventional chemotherapy resulting in a long-term overall survival (OS) of approximately 10% (2, 3). On November 22, 2013, FDA approved sorafenib (Nexavar, Bayer HealthCare) for the treatment of radiation-refractory, progressive, DTC, based on the results of a randomized, placebo-controlled trial ($n = 471$) that demonstrated a statistically significant improvement in progression-free survival [PFS; HR, 0.59; 95% confidence interval (CI), 0.45–0.76; $P < 0.001$, two-sided stratified log-rank test] with median PFS times of 10.8 months in the sorafenib arm and 5.8 months in the placebo arm.

Lenvatinib is an oral, multiple receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of the VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4, the platelet-derived growth factor receptor alpha (PDGFR α), KIT, and RET. A single randomized controlled trial [E7080-G000-303 or SELECT (herein referred to as Study 303)] along with a safety database of 1,108 patients who were exposed to lenvatinib in various clinical trials was submitted to support the U.S. approval. The results of this trial have been published (4). This article summarizes FDA's review of the data submitted in the application, the issues identified during the review, and the basis for FDA approval.

¹Office of Hematology and Oncology Products, Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland. ²Office of Clinical Pharmacology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland. ³Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland. ⁴Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland.

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P. Keegan and R. Pazdur share senior authorship.

Corresponding Author: Abhilasha Nair, FDA, 10903 New Hampshire Avenue, White Oak Building 22, Room 2362, Silver Spring, MD 20993. Phone: 301-796-8317; Fax: 301-796-9849; E-mail: Abhilasha.Nair@fda.hhs.gov

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Nair et al.

Clinical Trial

Study 303 was a multicenter, randomized (2:1), double-blind, placebo-controlled trial. Study 303 enrolled patients with locally recurrent or metastatic RAI-refractory DTC who had radiographic evidence of progression within 12 months prior to randomization. Patients were enrolled at one of 117 sites in Europe, North America, Asia, or Latin America during the period of August 5, 2011, to October 4, 2012. The protocol defined RAI-refractory as one or more measurable lesions without iodine uptake on RAI scan, iodine uptake but with progression within 12 months of RAI therapy, or having received cumulative RAI activity of >600 mCi (22 GBq) with the last dose administered at least 6 months prior to study entry. Patients were randomly allocated to receive lenvatinib 24 mg once daily ($n = 261$) or placebo ($n = 131$). Randomization was stratified by geographic region (Europe, North America, or other), prior VEGF/VEGFR-targeted therapy (yes or no), and age (≤ 65 years or >65 years). The pre-specified major efficacy outcome measure was independent radiologic review-determined PFS using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The study employed real-time independent review of radiographs to reduce bias and reduce the chance of the results being influenced by informative censoring. The study was designed to require a total of 214 PFS events for 90% power to identify a PFS improvement of approximately 6 months (HR, 0.57) at a two-sided significance level of 0.01. Other efficacy outcome measures included objective response rate (ORR) and OS. The protocol allowed patients who were allocated to receive placebo to receive open-label lenvatinib following independent review confirmation of disease progression.

Patient Characteristics

The median age of the 392 randomly allocated patients was 63 years; 51% were men; 79% were white; 54% had an ECOG performance status of 0; and 24% had received 1 prior VEGF/VEGFR-targeted therapy. Almost all patients had metastatic disease (99%). Metastatic disease was present in the lungs in 89% of patients, lymph nodes in 52%, bone in 39%, liver in 18%, and brain in 4%. Approximately two thirds of patients (66%) had papillary thyroid cancer and 34% had follicular thyroid cancer. Prior to study entry, patients received a median cumulative RAI activity of 350 mCi (12.95 GBq). Following progression, 83% of patients randomly assigned to receive placebo crossed over to receive open-label lenvatinib.

Efficacy Results

A statistically significant prolongation of PFS as determined by real-time independent radiology review was demonstrated in Study 303 (HR, 0.21; 95% CI, 0.16–0.28; $P < 0.001$). Median PFS was 18.3 months in the lenvatinib arm compared with 3.6 months in the placebo arm (see Table 1 and Fig. 1). ORRs were 65% (95% CI, 59%–71%) and 2% (95% CI, 0%–4%) in the lenvatinib and placebo arms, respectively. Most patients experienced a partial response; however, 2% of patients in the lenvatinib arm experienced a complete response. No statistically significant difference in OS between the two arms was demonstrated, although the point estimate for survival (HR) favored the lenvatinib arm.

Table 1. Primary efficacy results

	Lenvatinib N = 261	Placebo N = 131
PFS (IRR)		
Median PFS in months (95% CI)	18.3 (15.1–NR)	3.6 (2.2–3.7)
HR (95% CI) ^a	0.21 (0.16–0.28)	
P value ^b	<0.001	
ORR ^c		
ORR (95% CI)	65% (59–71)	2% (0–4)
P value ^c	<0.001	
OS		
Median OS in months (95% CI)	NR (22.1–NR)	NR (20.3–NR)
HR (95% CI) ^a	0.73 (0.50–1.07)	
P value ^c	0.10	

Abbreviations: IRR, independent radiology review; NR, not reached.

^aCox proportional hazard model 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).

^bCochran–Mantel–Haenszel χ^2 test.

^cLog-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).

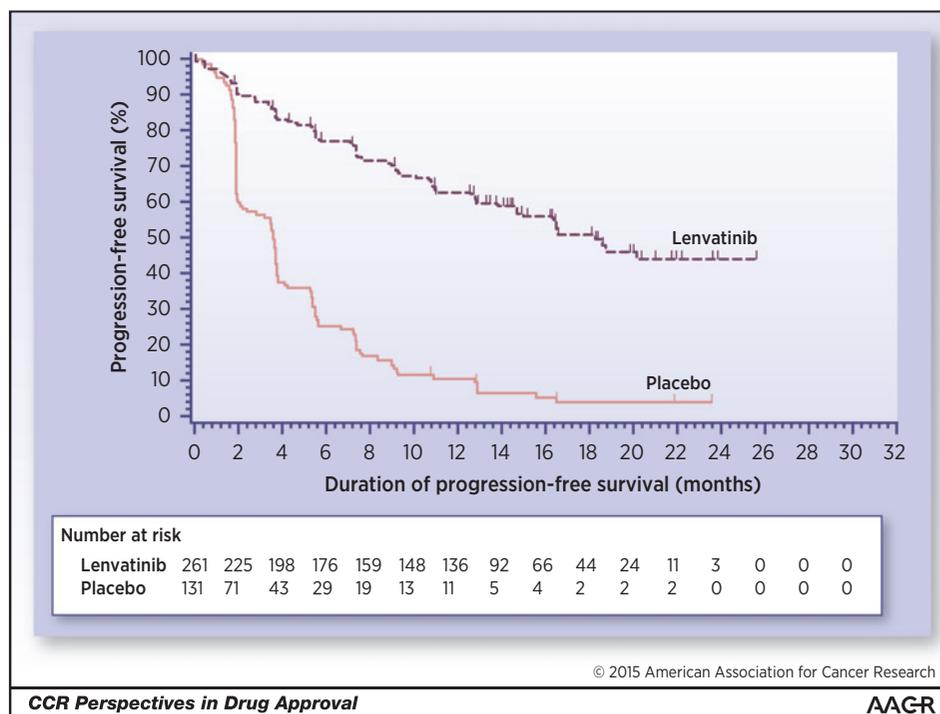
Safety Results

The FDA reviewed data from 1,108 patients with advanced solid tumors who received lenvatinib as a single-agent across multiple clinical studies including the 392 patients who were randomly allocated to receive lenvatinib in Study 303. In Study 303, the most common adverse reactions, some of which represent composite terms (e.g., fatigue was a composite term for asthenia, fatigue, and malaise), in order of decreasing frequency, observed in lenvatinib-treated patients compared with placebo were hypertension (73% vs. 16%), fatigue (67% vs. 35%), diarrhea (67% vs. 17%), arthralgia/myalgia (62% vs. 28%), decreased appetite (54% vs. 18%), decreased weight (51% vs. 15%), nausea (47% vs. 25%), stomatitis (41% vs. 8%), headache (38% vs. 11%), vomiting (36% vs. 15%), proteinuria (34% vs. 3%), palmar-plantar erythrodysesthesia (PPE) syndrome (32% vs. 1%), abdominal pain (31% vs. 11%), and dysphonia (31% vs. 5%). Hemorrhagic events occurred in 35% of patients treated with lenvatinib versus 18% who received placebo. Lenvatinib use also resulted in increased thyroid-stimulating hormone (TSH) levels; the etiology of this increase is not understood. In patients with normal TSH levels at baseline, 57% of lenvatinib-treated patients versus 14% of patients who received placebo had a TSH level greater than 0.5 mU/L.

Adverse reactions leading to dose reductions occurred in 68% of patients receiving lenvatinib and 5% of patients receiving placebo; 18% of patients discontinued lenvatinib and 5% discontinued placebo for adverse reactions. The most common adverse reactions (at least 10%) resulting in dose reductions of lenvatinib were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%). Grade 3 to 4 adverse events also occurred more frequently in the lenvatinib arm (see discussion below).

Other serious but less common adverse reactions (lenvatinib vs. placebo) included cardiac dysfunction [7% vs. 2% (\geq grade 3: 2% vs. 0%)]; arterial thrombotic events (5% vs. 2%); hepatotoxicity (\geq grade 3 increased ALT 4% vs. 0%); renal impairment [14% vs. 2% (\geq grade 3: 3% vs. 1%)]; gastrointestinal perforation or fistula (2% vs. 0.8%); QT/QTc prolongation [9% vs. 2% (\geq grade 3: 2% vs. 0%)]; and \geq grade 3 hypocalcemia

Figure 1.
Kaplan-Meier plot of PFS
(independent radiology review).



(9% vs. 2%). Some residual uncertainty exists regarding the true magnitude of the increased risk of these less common adverse reactions due to differences in the duration of observation for adverse events between arms from randomization until disease progression.

Discussion

The primary issues related to the lenvatinib New Drug Application (NDA) were whether the application should be granted priority review; whether the results of a single adequate and well-controlled trial demonstrated substantial evidence of effectiveness; whether the risk-benefit profiles of lenvatinib were favorable for the intended indication; and whether the optimal dose was identified during development to maximize the risk-benefit profile. The review of the lenvatinib NDA was designated as a priority review, in part, because antitumor activity was observed in a stratified subpopulation of patients representing an unmet medical need who were previously exposed to VEGF-targeted agents including sorafenib (comprising 25% of patients in the lenvatinib arm and 21% of patients in the placebo arm). 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.

FDA Guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998) describes the conditions under which it is acceptable to rely on the results of a single study (5). These include an effect on a clinically important endpoint such as mortality or major morbidity, large multicenter study, consistency across subsets, multiple studies in a single study, multiple endpoints involving different events, and a statistically very persuasive finding (5). Although the primary endpoint of Study 303 was PFS and not mortality as described in the Guidance, FDA was confident that the effect was a real effect based

on the magnitude of the effect on PFS observed in the clinical trial; small *P* value (with a pre-specified two-sided alpha of 0.01); and consistent results across multiple subsets (with 95% CIs for the HRs excluding 1.0). FDA determined that it would not be appropriate to require a second trial and delay access to lenvatinib, given the magnitude of the effect size and statistically robust findings observed in Study 303.

The third major issue pertinent to this application was whether the risk-benefit profile of lenvatinib was favorable for the intended indication. FDA Guidance (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007) states that whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit profile of the new treatment (6). In Study 303, a statistically robust PFS effect was observed with an HR of 0.21 (0.16–0.28) and *P* value of <0.001. This translated into an improvement in median PFS of almost 15 months. The point estimate for OS favored the lenvatinib arm but was not statistically significant (HR, 0.073; 95% CI, 0.050–1.07); however, based on these results, although a detriment in OS cannot formally be excluded, a detriment is *unlikely* based on the OS findings in Study 303. Also relevant in the assessment of survival was that the results were immature (approximately 70% of patients were censored) and that 83% of patients allocated to placebo crossed over to receive lenvatinib and antitumor activity was observed in these patients at crossover. The relatively long survival (compared with other patients with different metastatic adenocarcinomas) and crossover may challenge the ability to detect a statistically significant survival result in such a setting.

The improvement in PFS must be assessed in light of toxicities observed with lenvatinib including an estimated incidence rate of the following grade 3 or 4 adverse reactions (lenvatinib vs. placebo): hypertension (44% vs. 4%); decreased weight (13% vs. 1%); fatigue (11% vs. 4%); proteinuria (11% vs. 0); diarrhea

Nair et al.

(9% vs. 0); decreased appetite (7% vs. 1%); stomatitis (5% vs. 0); and arthralgia/myalgia (5% vs. 3%). These and other common adverse reactions were generally manageable with dose reduction, and dose reductions occurred in 68% of patients receiving lenvatinib. Lenvatinib can also increase the risk for serious but less common adverse reactions, including cardiac dysfunction, arterial thrombotic events, hepatotoxicity, renal impairment, gastrointestinal perforation and fistula, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, and impairment of TSH suppression. Many of these serious toxicities have also been observed with other tyrosine kinase inhibitors. Uncertainty exists regarding the true magnitude of risk for these less common toxicities due to differences in follow-up between arms in Study 303. In addition, FDA has also approved sorafenib, a drug that causes similar adverse events, for the treatment of RAI-refractory DTC based on an effect on PFS.

In summary, based on the magnitude of the effect on PFS (HR of 0.21), the point estimate observed for OS with a crossover rate of 83%, and high number of responders (including patients previously treated with sorafenib), Study 303 provided data to support a favorable risk-benefit profile for lenvatinib given that the more common severe toxicities were managed with dose reduction. Nevertheless, physicians should be aware of the overall adverse reaction profile of lenvatinib to determine if lenvatinib is appropriate for their individual patient.

One additional issue pertinent to the review of this application was whether the dose of lenvatinib administered in Study 303 was the optimal dose from a risk-benefit standpoint given that 68% of patients receiving lenvatinib required a dose reduction due to an adverse event. Although the applicant provided a sound rationale for investigating the 24 mg dose (including the substantial activity observed at this dose), too few patients with DTC were treated with lower doses to determine whether a lower dose could provide for an improved safety/tolerability profile while also preserving efficacy. Lenvatinib activity was observed at the 20 mg dose in 27 patients who crossed over from placebo in Study 303 (ORR of 44%); however, too few patients received this dose to

make formal conclusions. Ultimately, Eisai will conduct a clinical trial as a postmarketing requirement in order to investigate whether lower doses of lenvatinib will result in a decreased incidence of serious and severe adverse reactions while also evaluating the antitumor activity of lenvatinib.

In conclusion, residual uncertainty exists regarding the optimal dose of lenvatinib that will confer the most favorable risk-benefit profile. However, FDA approved lenvatinib based on the magnitude of the treatment effect in delaying progression, without a detrimental effect on survival, supported by a safety profile that resembles other approved "promiscuous" tyrosine kinase inhibitors which primarily consists of toxicities that a practicing oncologist is familiar with and can be managed effectively by prompt dose interruption or dose modification.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A. Nair, S.J. Lemery, L. Zhou, R. Pazdur

Development of methodology: A. Nair, L. Zhao, R. Pazdur

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L. Zhao, H. Zhao

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Nair, S.J. Lemery, J. Yang, L. Zhao, X. Jiang, K. He, E. Fox, P. Keegan

Writing, review, and/or revision of the manuscript: A. Nair, S.J. Lemery, J. Yang, A. Marathe, L. Zhao, X. Jiang, K. He, G. Ladouceur, A.K. Mitra, L. Zhou, E. Fox, S. Aungst, W. Helms, P. Keegan, R. Pazdur

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Zhao, K. He, R. Pazdur

Other (reviewed the CMC section leading to the marketing approval of the drug product): A.K. Mitra

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