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Eisai Co., Ltd.

ANTICANCER AGENT LENVATINIB PHASE III TRIAL RESULTS PUBLISHED IN NEW ENGLAND JOURNAL OF MEDICINE

SIGNIFICANT IMPROVEMENT IN PROGRESSION-FREE SURVIVAL SHOWN IN PATIENTS WITH RADIOIODINE-REFRACTORY DIFFERENTIATED THYROID CANCER

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the results from the Phase III SELECT trial of lenvatinib mesylate (lenvatinib), a novel investigative anticancer agent for patients with progressive radioiodine-refractory differentiated thyroid cancer (RR-DTC), were published in the *New England Journal of Medicine* (NEJM) on February 12, 2015. This marks the first time that a journal article on a Phase III trial of a systemic therapy in thyroid cancer has been published in the NEJM.

The SELECT study was a multicenter, randomized, double-blind, placebo-controlled Phase III study of 392 patients with progressive RR-DTC. In the study's primary endpoint of progression-free survival (PFS), lenvatinib demonstrated a statistically significant extension in PFS compared to placebo ($p<0.001$; median PFS in the lenvatinib group: 18.3 months, median PFS in the placebo group: 3.6 months; Hazard Ratio (HR) 0.21 [99% CI: 0.14-0.31]). In addition, lenvatinib showed a statistically significant improvement in response rate (sum of complete and partial responses) compared to placebo ($p<0.001$; lenvatinib: 64.8%, placebo: 1.5%). In particular, complete response was observed in 1.5% (4 patients) of the lenvatinib group and zero in the placebo group. The most common lenvatinib treatment-related adverse events of any grade, which occurred in more than 40% of patients in the lenvatinib group, were hypertension (67.8%), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), weight loss (46.4%) and nausea (41.0%).

Lenvatinib is an oral molecular targeted agent that selectively inhibits the activities of several different molecules including VEGFR, FGFR, RET, KIT and PDGFR. In particular, the agent simultaneously inhibits VEGFR, FGFR and also RET which are especially involved in tumor angiogenesis and proliferation of thyroid cancer. Furthermore, lenvatinib has been confirmed through X-ray crystal structural analysis to be the first compound to demonstrate a new binding mode (Type V) to VEGFR2, and exhibits rapid and potent inhibition of kinase activity, according to kinetic analysis[1].

Eisai has already submitted regulatory applications for lenvatinib seeking approval for refractory thyroid cancer to health authorities firstly in Japan in June 2014, both the United States and the EU in August 2014, and is filing subsequent applications in other countries worldwide. Lenvatinib was granted Orphan Drug Designation for thyroid cancer by regulatory authorities in Japan, the United States and Europe. In addition, lenvatinib was granted priority review status in the United States and accelerated assessment in Europe. Furthermore, Eisai is conducting a global Phase III trial of lenvatinib in hepatocellular carcinoma and as well as Phase II studies of lenvatinib in several other tumor types such as renal cell carcinoma and non-small cell lung cancer.

Differentiated thyroid cancer is the most common form of thyroid cancer and accounts for approximately 95% of all thyroid cancers. Among differentiated thyroid cancers, some are radioiodine-refractory (RR-DTC) and cannot easily be cured with surgery and radioactive iodine treatment, which presents a significant unmet medical need as treatment options are limited for RR-DTC. Eisai is committed to exploring the potential clinical benefits of lenvatinib in order to further contribute to patients with cancer, including patients with thyroid cancer, and their families.

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[Notes to editors]

1. About Lenvatinib (E7080)

Lenvatinib, discovered and developed by Eisai, is an oral multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3 (FLT4)), in addition to other proangiogenic and oncogenic pathway-related RTKs (including fibroblast growth factor (FGF) receptors FGFR1, 2, 3 and 4; the platelet-derived growth factor (PDGF) receptor PDGFRα; KIT; and RET) involved in tumor proliferation. In particular, the agent simultaneously inhibits VEGFR, FGFR and also RET which are especially involved in tumor angiogenesis and proliferation of thyroid cancer. Furthermore, lenvatinib has been confirmed through X-ray crystal structural analysis to be the first compound to demonstrate a new binding mode (Type V) to VEGFR2, and exhibits rapid and potent inhibition of kinase activity, according to kinetic analysis[1]. Eisai has already submitted regulatory applications for lenvatinib seeking indication approval for refractory thyroid cancer to health authorities firstly in Japan in June 2014, followed by the United States, the EU, Switzerland, South Korea, Canada, Singapore, Russia, Australia and Brazil. Meanwhile, Eisai is currently conducting clinical studies of lenvatinib in several types of cancer including hepatocellular carcinoma (Phase III), renal cell carcinoma (Phase II), non-small cell lung cancer (Phase II) and endometrial cancer (Phase II). Furthermore, lenvatinib has been granted Orphan Drug Designation in Japan (for thyroid cancer), the United States (for the treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer), and Europe (for follicular and papillary thyroid cancer).

2. About Lenvatinib's Novel Binding Mode (Type V)[1]

Kinase inhibitors are categorized into several types (Type I to Type V) depending on the binding site and the conformation of the targeted kinase in complex with them. Most of the currently approved tyrosine kinase inhibitors are either Type I or Type II, however according to X-ray crystal structural analysis, lenvatinib was found to possess a new Type V binding mode of kinase inhibition that is distinct from existing compounds. In addition, lenvatinib was confirmed via kinetic analysis to exhibit rapid and potent inhibition of kinase activity, and it is suggested that this may be attributed to its novel binding mode.

3. About the SELECT study

The SELECT (**S**tudy of (**E**7080) **LE**nvatinib in Differentiated **C**ancer of the **T**hyroid) study was a multicenter, randomized, double-blind, placebo-controlled Phase III study to compare the progression-free survival (PFS) of patients with radioactive iodine-refractory differentiated thyroid cancer and radiographic evidence of disease progression within the prior 13 months, treated with once-daily, oral lenvatinib (24mg) versus placebo. Participants were randomized 2:1 to either lenvatinib or placebo therapy. The primary endpoint was PFS assessed by independent radiologic review. The secondary endpoints of the study included overall response rate (ORR), overall survival (OS) and safety. The study enrolled 392 patients in over 100 sites in Europe, North and South America and Asia, including Japan,and was conducted by Eisai in collaboration with SFJ Pharma Ltd.

4. About Thyroid Cancer

Thyroid cancer refers to cancer that forms in the tissues of the thyroid gland, located at the base of the throat near the trachea. It is more common in women than in men and usually occurs between the ages of 25 and 65. The most common types of thyroid cancer, papillary and follicular (including Hürthle cell), are classified as differentiated thyroid cancer and account for approximately 95% of all cases. The remaining cases are classified as either undifferentiated (3-5% of cases) or medullary carcinoma (1-2% of cases). While most differentiated thyroid cancer patients are curable with surgery and radioactive iodine treatment, there are a small percentage of patients for which these types of therapies are not suitable.

5. About the SFJ Pharmaceuticals Group

The SFJ Pharmaceuticals Group, which includes SFJ Pharma Ltd., is a global drug development company, which provides a unique co-development partnering model for some of the world's top pharmaceutical and biotechnology companies. SFJ uses its financial strength and core team of pharmaceutical development experts to provide highly customized partnering models in which SFJ provides the funding and clinical development supervision, necessary to obtain regulatory approval for some of the most promising drug development programs of pharmaceutical and biotechnology companies.

[1] Okamoto K, et al. Distinct Binding Mode of Multikinase Inhibitor Lenvatinib Revealed by Biochemical Characterization. *ACS Med. Chem. Lett.;* 2015, 6, 89–94