No.15-39

June 1, 2015
Eisai Co., Ltd.

EISAI RECEIVES EUROPEAN COMMISSION APPROVAL OF ANTICANCER AGENT LENVIMA® FOR TREATMENT OF ADVANCED THYROID CANCER REFRACTORY TO RADIOACTIVE IODINE

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its U.K. subsidiary Eisai Europe Ltd. has received approval from the European Commission (EC) for anticancer agent Lenvima® (lenvatinib mesylate) in the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI). Lenvima was granted an accelerated assessment by the European Medicines Agency, and was ultimately approved in approximately 9 months since the application was filed on August 14, 2014.

The decision by the EC was based on the results of a multicenter, randomized, double-blind, placebo-controlled Phase III study (the SELECT study) on progressive RAI refractory DTC[1]. In the study's primary endpoint of progression-free survival (PFS), Lenvima demonstrated a statistically significant extension in PFS compared to placebo ($p<0.001$; median PFS in the Lenvima 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, the study underlines the rapid response of Lenvima, with a median time to first objective response of 2.0 months. Furthermore, Lenvima demonstrated a statistically significant improvement in objective response rate (number of objective responders [%]) compared to placebo ($p<0.001$; Lenvima: 64.8% vs placebo: 1.5%). In particular, complete response was observed in 1.5% (4 patients) of the Lenvima group and none in the placebo group. The most common Lenvima treatment-related adverse events were hypertension, diarrhea, fatigue or asthenia, decreased appetite, weight loss and nausea.

Discovered at Eisai's Tsukuba Research Laboratories and developed in-house, Lenvima is an orally administered 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 RET, which are especially involved in tumor angiogenesis and proliferation of thyroid cancer. Furthermore, Lenvima has been confirmed through X-ray co-crystal structural analysis to demonstrate a new binding mode (Type V) to VEGFR2, and exhibits potent inhibition of kinase activity and rapid binding to the target molecule according to kinetic analysis[2].

Lenvima was launched in the United States indicated for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer in February 2015. In addition, Lenvima was approved in Japan for the treatment of unresectable thyroid cancer in March 2015.

Thyroid cancer affects more than 52,000 people in Europe each year. Although treatment is possible for most types of thyroid cancer, there are few treatment options available once thyroid cancer has progressed, therefore it remains a disease with significant unmet medical needs. Eisai is committed to exploring the potential clinical benefits of Lenvima in order to further contribute to patients with cancer and their families.

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[Notes to editors]

1. About Lenvima (lenvatinib mesylate)

Lenvima, discovered and developed by Eisai, is an orally administered 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, VEGFR2 and VEGFR3), 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, Lenvima 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[2]. Lenvima is approved for the treatment of refractory thyroid cancer in the United States, Japan as well as Europe, and is currently undergoing regulatory review in seven other countries. Meanwhile, Eisai is currently conducting clinical studies of Lenvima 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, Lenvima was granted Orphan Drug Designation in Japan for thyroid cancer, in the United States for treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer and in Europe for follicular and papillary thyroid cancer.

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

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, Lenvima was found to possess a new Type V binding mode of kinase inhibition that is distinct from existing compounds. In addition, Lenvima was confirmed via kinetic analysis to exhibit rapid binding to the target molecule 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 Lenvima (24mg) versus placebo. Participants were randomized 2:1 to either Lenvima or placebo therapy. The primary endpoint was PFS assessed by independent radiologic review. The secondary endpoints of the study included response rate (sum of complete and partial responses), 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. 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.

[1] Schlumberger M, et al. Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. *N. Engl. J. Med*. 2015; 372, 621–630

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