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Eisai Co., Ltd.

EISAI RECEIVES APPROVAL FOR ANTICANCER AGENT LENVIMA® IN SOUTH KOREA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has received marketing approval of its novel in-house developed anticancer agent Lenvima® (lenvatinib mesylate) as a treatment for patients with progressive, locally recurrent or metastatic, differentiated thyroid carcinoma (DTC), refractory to radioactive iodine (RAI) from the regulatory authority in South Korea (Ministry of Food and Drug Safety). The marketing authorization application for Lenvima in South Korea was submitted in November 2014, and through the approval of this application, South Korea is the first country in Asia where Lenvima has been approved following Japan, the United States and Europe.

The decision to approve Lenvima in South Korea was based on the results of a pivotal Phase III study (the SELECT study) on DTC. In the study, Lenvima demonstrated a statistically significant extension in progression-free survival compared to placebo, as well as a high objective response rate.[1] 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 also 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 rapid binding to the target molecule and potent inhibition of kinase activity, according to kinetic analysis[2].

Lenvima has already been launched in Japan, the United States and Europe, while in Asia, applications seeking marketing approval are undergoing regulatory review in Singapore, Macao, Hong Kong, Taiwan, Malaysia, India and Indonesia. Furthermore, Eisai is conducting a global Phase III study of Lenvima in hepatocellular carcinoma as well as Phase II studies of Lenvima in several other tumor types such as renal cell carcinoma and non-small cell lung cancer.

The number of patients newly diagnosed with thyroid cancer in 2012 in South Korea was estimated to be 33,000, and in Asia was estimated to be 144,000. 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.

Together with providing Lenvima as a new treatment option for thyroid cancer to patients in South Korea, Eisai is working to obtain marketing approval in each country in Asia. Furthermore, Eisai is committed to exploring the potential clinical benefits of Lenvima in order to further contribute to patients with thyroid cancer, and their families.

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[Notes to editors]

1. About Lenvima (lenvatinib mesylate)

Lenvima 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) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including 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 co-crystal structural analysis to demonstrate a new binding mode (Type V) to VEGFR2, and exhibits rapid binding to the target molecule and potent inhibition of kinase activity, 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, and launched in Japan indicated for the treatment of unresectable thyroid cancer in May 2015. The agent was launched in the U.K. as the first country in Europe for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma refractory to radioactive iodine in June 2015. In addition, Lenvima is currently undergoing regulatory review in various countries around the world including in Asia, Canada, Russia, Australia Brazil and Mexico.

Meanwhile, Eisai is conducting a global Phase III study of Lenvima in hepatocellular carcinoma as well as Phase II studies of Lenvima in several other tumor types such as renal cell carcinoma and non-small cell lung cancer.

2. About the SELECT Study

The SELECT (Study of (E7080) LEnvatinib in Differentiated Cancer of the Thyroid) 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. Patients 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. In the study, 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 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. Lenvima also demonstrated a statistically significant improvement in response rate 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 zero in the placebo group. The most common Lenvima treatment-related adverse events of any grade, which occurred in more than 40% of patients in the Lenvima 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%).

3. 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, a small percentage of patients do not respond to therapy.

[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