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Eisai Co., Ltd.

EISAI LAUNCHES ANTICANCER AGENT LENVIMA® (LENVATINIB MESYLATE) IN UNITED KINGDOM INDICATED FOR 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 launched its in-house developed novel anticancer agent Lenvima® (lenvatinib mesylate) indicated for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma (DTC) refractory to radioactive iodine (RAI) in the United Kingdom. Following the launch of Lenvima in the United Kingdom, Eisai plans to launch the agent in countries throughout Europe.

It is estimated that thyroid cancer affects more than 52,000 people in Europe each year. Differentiated thyroid cancer is the most common form of thyroid cancer and accounts for approximately 95% of all thyroid cancers. Although most differentiated thyroid cancers can be treated with surgery and radioactive iodine treatment, there are few treatment options available once the cancer has progressed, therefore it remains a disease with significant unmet medical needs.

In a global Phase III study (the SELECT study) of Lenvima in differentiated thyroid cancer, Lenvima demonstrated a statistically significant extension in progression free survival and improved response rates compared to placebo [1]. The most common Lenvima treatment-related adverse events were hypertension, diarrhea, fatigue or asthenia, decreased appetite, weight loss and nausea. Lenvima was granted an accelerated assessment by the European Medicines Agency, and was approved on May 28, 2015.

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 was first 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 was subsequently launched in Japan for the treatment of unresectable thyroid cancer in May 2015. Eisai is aiming to launch the agent in over 20 countries in fiscal 2015. 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.

In addition to providing Lenvima as a new treatment option for thyroid cancer, Eisai is committed to exploring the potential clinical benefits of Lenvima in order to further contribute to, and address the diverse needs of, patients with 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 approved by the European Commission for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma refractory to radioactive iodine in May 2015. In addition, Lenvima is currently undergoing regulatory review in Switzerland, South Korea, Canada, Singapore, Russia, Australia and Brazil.

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 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. 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%).

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