

EISAI RECEIVES APPROVAL IN JAPAN FOR ANTICANCER AGENT LENVIMA[®] (LENVATINIB MESYLATE) AS TREATMENT FOR UNRESECTABLE THYROID CANCER

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has received manufacturing and marketing authorization in Japan for its in-house developed novel anticancer agent Lenvima[®] (lenvatinib mesylate) indicated for the treatment of unresectable thyroid cancer.

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 placebo¹. In the SELECT study, the five most common Lenvima treatment-related adverse events of any grade were hypertension, diarrhea, fatigue or asthenia, decreased appetite, and weight loss. Furthermore, a Phase II study (Study 208) conducted in Japan suggested efficacy and tolerability of Lenvima in medullary thyroid carcinoma and anaplastic thyroid carcinoma as well². Due to the results of these studies, Lenvima is the first molecular targeted treatment in Japan approved with an indication for unresectable thyroid cancer which covers differentiated thyroid cancer as well as medullary thyroid carcinoma and anaplastic thyroid carcinoma.

The number of patients with thyroid cancer in Japan is estimated to be between 13,000 and 29,000. Although treatment is possible for most types of thyroid cancer, there are few treatment options available for unresectable thyroid cancer and so there is a pressing need for the development of new treatment options. With a high degree of clinical malignancy and a prognosis among the worst of all types of cancer, anaplastic thyroid carcinoma in particular is a disease with significant unmet medical needs. Through this approval, Eisai hopes that Lenvima will make a contribution to patients as a new standard treatment for unresectable thyroid cancer, which has no established standard treatment in Japan at present.

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 analysis³.

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. Currently, the agent is undergoing regulatory review in the EU, as well as Switzerland, South Korea, Canada, Singapore, Russia, Australia and Brazil. Furthermore, Eisai is conducting a global Phase III trial 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, in accordance with the conditions of approval, Eisai will work after launch to carry out an observational study and promote the appropriate use of Lenvima. Eisai is committed to exploring the potential clinical benefits of Lenvima in order to further contribute to patients with cancer, and their families.

Media Inquiries:
Public Relations Department,
Eisai Co., Ltd.
+81-(0)3-3817-5120

[Notes to editors]

1. Product Outline

1) Product name

Lenvima[®] Capsule 4 mg, Lenvima[®] Capsule 10 mg

2) Generic name

Lenvatinib mesylate

3) Indication for use

Unresectable thyroid cancer

4) Dosage and administration

The usual adult dose of lenvatinib is 24 mg administered orally once a day. The dose may be reduced depending on the condition of the individual patient.

2. 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 PDGFR α ; 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 analysis¹. Lenvima has been approved for the treatment of refractory thyroid cancer in the United States and Japan, and is currently undergoing regulatory review for this indication in the EU, Switzerland, South Korea, Canada, Singapore, Russia, Australia and Brazil. 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.

3. About Lenvima's Novel Binding Mode (Type V)³

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 and potent inhibition of kinase activity, and it is suggested that this may be attributed to its novel binding mode.

4. About the SELECT study¹

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. 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. 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 (HR) 0.21 [99% CI: 0.14-0.31]). In addition, Lenvima demonstrated a statistically significant improvement in response rate (sum of complete and partial responses) 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%).

5. 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.

6. About the Results of Study 208 Conducted in Japan and Presented at the 39th European Society of Medical Oncologists Congress²

Study 208 was a multi-center, open label, non-randomized, single-arm Phase II clinical study to evaluate the safety, efficacy, and pharmacokinetics of Lenvima when orally administered once daily in patients with radioiodine-refractory differentiated thyroid cancer (RR-DTC), unresectable medullary thyroid carcinoma (MTC) or unresectable anaplastic thyroid carcinoma (ATC). The study enrolled 35 patients (RR-DTC: 22 patients, MTC: 4 patients, ATC: 9 patients) between September 2012 and September 2013. Responses were observed in all three types of thyroid cancer. The most commonly reported adverse events in the study were hypertension, palmar-plantar erythrodysesthesia syndrome, fatigue, decreased appetite, proteinuria and stomatitis.

¹ Schlumberger M, et al. Lenvatinib versus Placebo in Radioiodine-refractory Thyroid Cancer. *N Engl J Med.* 2015; 327, 621-630.

² Takahashi S, et al. Phase II Study of Lenvatinib, a Multi-targeted Tyrosine Kinase Inhibitor, in Patients with all Histologic Subtypes of Advanced Thyroid Cancer (Differentiated, Medullary and Anaplastic). *ESMO Meeting Abstr.* 2014; 4933.

³ Okamoto K, et al. Distinct Binding Mode of Multikinase Inhibitor Lenvatinib Revealed by Biochemical Characterization. *ACS Med. Chem. Lett.*; 2015, 6, 89-94