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Eisai Co., Ltd.

EISAI'S IN-HOUSE DEVELOPED NOVEL ANTICANCER AGENT LENVIMA® RECEIVES BREAKTHROUGH THERAPY DESIGNATION FROM U.S. FDA FOR RENAL CELL CARCINOMA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today its U.S. subsidiary Eisai Inc. has received a Breakthrough Therapy designation from the U.S. Food and Drug Administration (FDA) for its in-house developed novel anticancer agent Lenvima® (lenvatinib mesylate, "lenvatinib") for the potential indication of advanced and/or metastatic renal cell carcinoma.

The Breakthrough Therapy designation is an U.S. FDA program intended to expedite development and review of drugs for serious or life-threatening conditions. The benefits of this designation include more intensive guidance on an efficient drug development program and submission strategy, as well as eligibility for rolling review. Preliminary clinical evidence demonstrating the drug may have substantial improvement on at least one clinically significant endpoint over available therapy is required for Breakthrough Therapy designation.

This Breakthrough Therapy designation was based on the results of a Phase II clinical trial (Study 205)[1] of lenvatinib in advanced or metastatic renal cell carcinoma following one prior vascular endothelial growth factor-targeted therapy. From the results of the study, the combination of lenvatinib plus everolimus demonstrated a significant extension in progression free survival (PFS), the study's primary endpoint, compared to everolimus alone. Additionally, lenvatinib alone demonstrated an extension in PFS compared to everolimus alone. Both the lenvatinib plus everolimus group and the lenvatinib alone group showed an improvement in objective response rate compared to the everolimus alone group. Furthermore, an updated analysis carried out in December 2014 suggested that lenvatinib plus everolimus extends overall survival compared to everolimus alone. The most common treatment-emergent adverse events (TEAE) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher included diarrhea, hypertension and fatigue.

The number of patients with kidney cancer in 2012 was estimated to be approximately 338,000 worldwide, including 58,000 in the United States.[2] Renal cell carcinoma comprises more than 90% of all malignancies of the kidney.[3] For advanced or metastatic renal cell carcinoma that is difficult to treat with surgery, the standard treatment method is molecular targeted drug therapy, however with low 5-year survival rates, this remains a disease with significant unmet medical needs. According to the results of Study 205, lenvatinib plus everolimus showed superior PFS over everolimus alone which is recommended by the National Comprehensive Cancer Network (NCCN) guidelines as a 2nd-line therapy for advanced or metastatic renal cell carcinoma. Currently, no combination therapy for this indication has been approved in the United States, Europe or Japan.

Eisai has shared the results of Study 205 with regulatory authorities to discuss further steps regarding potential submission strategies for an indication covering renal cell carcinoma. Eisai is committed to exploring the potential clinical benefits of lenvatinib in order to further contribute to patients with cancer and their families.

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[Notes to editors]

1. About lenvatinib mesylate (product name: Lenvima)

Lenvatinib 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. Lenvatinib 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.[4]

Currently, lenvatinib has been launched in the United States, Japan and Europe indicated for the treatment of refractory thyroid cancer. In addition, lenvatinib is currently undergoing regulatory review in nine countries around the world. Meanwhile, Eisai is conducting a global Phase III study of lenvatinib in hepatocellular carcinoma as well as Phase II studies of lenvatinib in several other tumor types such as endometrial carcinoma and non-small cell lung cancer. Furthermore, lenvatinib was granted Orphan Drug Designation by regulatory authorities in the United States, Japan and Europe for refractory thyroid cancer.

2. About Study 205[1]

Study 205 was a multicenter, randomized, open-label study of lenvatinib (18 mg) in combination with the anticancer agent everolimus (5 mg), lenvatinib alone (24 mg), and everolimus alone (10 mg) in patients with advanced or metastatic renal cell carcinoma following one prior VEGF-targeted therapy. 153 patients were randomized in a 1:1:1 ratio to one of three treatment arms to compare the safety and efficacy of these three regimens.

From the results of the study, the combination of lenvatinib plus everolimus demonstrated a significant extension in the study's primary endpoint of progression free survival (PFS) compared to everolimus alone (median PFS for the lenvatinib plus everolimus group: 14.6 months vs median PFS for the everolimus alone group: 5.5 months; Hazard Ratio (HR) 0.40 [95% CI: 0.24-0.68], p<0.001). Additionally, median PFS for lenvatinib alone was 7.4 months, demonstrating an extension in PFS compared to everolimus alone (HR: 0.61 [95% CI: 0.38-0.98]).

The study also assessed objective response rate (ORR) and overall survival (OS) as secondary endpoints. Regarding ORR, both the lenvatinib plus everolimus group and the lenvatinib alone group showed an improvement in ORR compared to the everolimus alone group (lenvatinib plus everolimus: 43%, lenvatinib alone: 27%, everolimus alone: 6%). Furthermore, regarding OS, an updated analysis carried out in December 2014 suggested that lenvatinib plus everolimus extends OS compared to everolimus alone (HR 0.51 [95% CI=0.30-0.88]).

The most common treatment-emergent adverse events (TEAE) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher (Common Terminology Criteria for Adverse Events) included diarrhea, hypertension and fatigue.

3. About Renal Cell Carcinoma

The number of patients with renal cancer was estimated to be approximately 338,000 worldwide, including approximately 17,000 in Japan, 58,000 in the United States and 115,000 in Europe.[2] Renal cell carcinoma comprises more than 90% of all malignancies of the kidney.[3] The incidence of renal cell carcinoma in people aged in their late 50s is rising, and is more likely to affect men than women. While the standard treatment method primarily consists of surgery, once the cancer has relapsed or metastasized, the main treatment method becomes chemotherapy using molecular targeted drugs.

4. About the Breakthrough Therapy Designation

The Breakthrough Therapy designation is a program intended to expedite development and review of drugs for serious or life-threatening conditions. Preliminary clinical evidence demonstrating the drug may have substantial improvement on at least one clinically significant endpoint over available therapy is required in order to qualify for this designation. The benefits of this Breakthrough Therapy designation include more intensive guidance on an efficient drug development program, access to a regulatory liaison to help accelerate review time, and eligibility for rolling review as well as priority review.

[1] Motzer, R, et al. Randomized phase II, three-arm trial of lenvatinib (LEN), everolimus (EVE), and LEN+EVE in patients (pts) with metastatic renal cell carcinoma (mRCC). *Journal of Clinical Oncology* 33(15), 2015 (suppl; abstract 4506)

[2] Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 http://globocan.iarc.fr/

[3] Eble J.N, ed. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. 3rd ed. *World Health Organization Classification of Tumours*, vol.7 (IARC, 2004)

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