

**EISAI SUBMITS NEW APPLICATION IN EUROPE FOR IN-HOUSE DEVELOPED  
ANTICANCER AGENT LENVATINIB SEEKING APPROVAL FOR INDICATION  
COVERING RENAL CELL CARCINOMA**  
*APPLICATION BASED ON RESULTS OF PHASE II CLINICAL STUDY*

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its European regional headquarters Eisai Europe Ltd. (Location: U.K.) has submitted a new application to the European Medicines Agency (EMA) for its in-house developed novel anticancer agent lenvatinib mesylate (generic name, "lenvatinib") for use in the treatment of advanced or metastatic renal cell carcinoma. As a new medicine that is expected to be of major public health interest, particularly from the viewpoint of therapeutic innovation, lenvatinib has been granted an accelerated review by the EMA.

The number of patients with renal cancer in Europe is estimated to be 115,000,<sup>1</sup> and renal cell carcinoma comprises more than 90% of all malignancies of the kidney.<sup>2</sup> 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 need.

This application was based on a Phase II clinical study (Study 205)<sup>3</sup> which compared the efficacy and safety among three groups including a combination of lenvatinib (18 mg) plus everolimus (5 mg), lenvatinib alone (24 mg) and everolimus alone (10 mg) in unresectable 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 group demonstrated a significant extension in progression free survival (PFS), the study's primary endpoint, compared to the everolimus alone group. Additionally, the lenvatinib alone group demonstrated an extension in PFS compared to the 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. The most common treatment-emergent adverse events (TEAEs) reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite and fatigue. The most common TEAEs of Grade 3 or higher were diarrhea, hypertension and fatigue.

Currently lenvatinib has been launched in the United States, Japan and Europe under the product name Lenvima<sup>®</sup> as a treatment for refractory thyroid cancer. In addition, lenvatinib has received a breakthrough therapy designation from the U.S. Food and Drug Administration for the potential indication of advanced and/or metastatic renal cell carcinoma, and an application seeking approval for an indication covering advanced or metastatic renal cell carcinoma was submitted in the United States in November 2015. Eisai intends to discuss further steps regarding potential submission strategies for this indication with the regulatory authorities in Japan as well.

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 (generic name, “lenvatinib”)

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 PDGFR $\alpha$ ; KIT; and RET) involved in tumor proliferation.

Currently, Eisai has obtained approval for lenvatinib in the United States, Japan, Europe, Korea and Canada as a treatment for refractory thyroid cancer, and is undergoing regulatory review throughout the world including in Asia, Russia, Australia, Brazil and Mexico. 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 biliary tract cancer.

### 2. About the Phase II Clinical Study (Study 205)<sup>3</sup>

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

From the results of the study, the combination of lenvatinib plus everolimus group demonstrated a significant extension in the study's primary endpoint of progression free survival (PFS) compared to the everolimus alone group (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],  $p=0.0005$ ). Additionally, median PFS for the lenvatinib alone group was 7.4 months, demonstrating an extension in PFS compared to the everolimus alone group (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 (TEAEs) 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) were 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 115,000 in Europe, 58,000 in the United States and 17,000 in Japan.<sup>1</sup> Renal cell carcinoma comprises more than 90% of all malignancies of the kidney,<sup>2</sup> and occurs when malignant cells are found in the lining of the tubules of the kidney. The incidence of renal cell carcinoma in people aged in their late 50s is rising, and is more likely to affect men than women. 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 need.

<sup>1</sup> Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, <http://globocan.iarc.fr/>

<sup>2</sup> 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)

<sup>3</sup> Motzer, R, et al. “Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial.” *The Lancet Oncology*, 2015; 16, 1473-1482.