

PHASE II TRIAL RESULTS ON NOVEL ANTICANCER AGENT LENVIMA® IN RENAL CELL CARCINOMA PUBLISHED IN THE LANCET ONCOLOGY

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the results of a Phase II clinical trial (Study 205)¹ of its in-house developed novel anticancer agent Lenvima® (lenvatinib mesylate, "lenvatinib") in advanced or metastatic renal cell carcinoma have been published in the online version of *The Lancet Oncology*¹, a leading clinical oncology research journal that is highly regarded worldwide.

Study 205 was a Phase II clinical trial to compare the safety and efficacy among three groups including a combination of lenvatinib (18 mg) plus everolimus (5 mg), lenvatinib alone (24 mg) and everolimus alone (10 mg) 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 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 group. 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 (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.

Renal cell carcinoma comprises more than 90% of all malignancies of the kidney.² 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, the combination of 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.

Lenvatinib has received a breakthrough therapy designation from the U.S. Food and Drug Administration (FDA) for the potential indication of advanced and/or metastatic renal cell carcinoma. Eisai has shared the results of Study 205 with the U.S. FDA and the European Medicines Agency to discuss further steps regarding potential submission strategies for an indication covering renal cell carcinoma, and Eisai intends to have similar discussions with the regulatory authorities in Japan as well. Currently lenvatinib has been launched in the United States, Japan and Europe indicated for refractory thyroid cancer, and clinical trials of the agent in various types of cancer such as hepatocellular carcinoma are also underway.

Eisai is committed to exploring the potential clinical benefits of lenvatinib 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. 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 PDGFR α ; 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.³

Currently, Eisai has obtained approval for lenvatinib in the United States, Japan, Europe and Korea indicated for the treatment of refractory thyroid cancer. In addition, lenvatinib is undergoing regulatory review throughout the world including in Asia, Canada, 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 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 205¹

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, 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 safety and efficacy 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], $p < 0.001$). 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 (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 58,000 in the United States, 17,000 in Japan and 115,000 in Europe.⁴ Renal cell carcinoma comprises more than 90% of all malignancies of the kidney,² 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 needs.

4. About The Lancet Oncology

Highly regarded worldwide, The Lancet Oncology is an influential medical journal specialized in the field of oncology.

- ¹ Motzer, R, et al. "Randomized phase II, three-arm trial of lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma." *The Lancet Oncology*, 2015.
[http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(15\)00290-9/abstract](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00290-9/abstract)
- ² 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)
- ³ Okamoto K, et al. Distinct Binding Mode of Multikinase Inhibitor Lenvatinib Revealed by Biochemical Characterization. *ACS Med. Chem. Lett.* 2015; 6, 89–94
- ⁴ Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 <http://globocan.iarc.fr/>