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Eisai Co., Ltd.

PHASE II TRIAL RESULTS ON ANTICANCER AGENT LENVIMA® IN RENAL CELL CARCINOMA TO BE DETAILED IN ORAL PRESENTATION AT 51ST ASCO ANNUAL MEETING

COMBINATION THERAPY WITH EVEROLIMUS DEMONSTRATES SIGNIFICANT EXTENSION IN PROGRESSION-FREE SURVIVAL

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that in the results of a Phase II clinical trial (Study 205) of its in-house developed anticancer agent Lenvima® (lenvatinib mesylate, "lenvatinib") in metastatic renal cell carcinoma, the combination of lenvatinib plus everolimus demonstrated a significant extension in progression free survival (PFS), the study's primary endpoint 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]). These data are to be presented today in an oral session at the 51st Annual Meeting of the American Society of Clinical Oncology (ASCO) taking place in Chicago, the United States.

Study 205 was an open-label, multicenter 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 metastatic renal cell carcinoma following one prior VEGF-targeted treatment. 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.

In addition to the primary endpoint of PFS, 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.

Renal cell carcinoma is the most common form of cancer to affect the kidneys. For metastatic or advanced 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.

"Additional treatments for metastatic renal cell carcinoma are needed for patients with this difficult-to-treat cancer," said Robert Motzer, M.D., Memorial Sloan Kettering Cancer Center, New York, and a principal investigator of the study. "These positive investigational study results show the potential role of lenvatinib in patients with metastatic renal cell carcinoma."

According to the results of this study, 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 unresectable advanced or metastatic renal cell carcinoma. Currently, no combination therapy for this indication has been approved in any major country worldwide.

Lenvatinib is an oral molecular targeted agent that selectively inhibits the activities of several different molecules including VEGFR, FGFR, RET, KIT and PDGFR, involved in angiogenesis and tumor proliferation. Lenvatinib has been approved in Japan, the United States and Europe indicated for the treatment of refractory thyroid cancer, and has been launched in Japan and the United States. The agent is undergoing regulatory review in seven other countries worldwide.

Eisai will share the results of Study 205 with regulatory authorities to discuss further steps regarding development and submission strategy 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 (lenvatinib mesylate)

Lenvatinib, discovered and developed by Eisai, is an oral molecular targeted agent that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1 (FLT1), VEGFR2 (KDR) and VEGFR3 (FLT4)), and fibroblast growth factor (FGF) receptors FGFR1, 2, 3 and 4 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. Furthermore, 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.[1] Lenvatinib has been approved in Japan, the United States and Europe indicated for the treatment of refractory thyroid cancer and the agent is undergoing regulatory review in seven other countries worldwide. It is currently under development as a potential treatment for hepatocellular carcinoma (Phase III), endometrial cancer (Phase II), non-small cell lung cancer (Phase II), renal cell carcinoma (Phase II) and other solid tumor types. Meanwhile, lenvatinib has been granted Orphan Drug Designation in Japan (for thyroid cancer), the United States (for the treatment of follicular, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer), and Europe (for follicular and papillary thyroid cancer).

2. About Lenvatinib's Novel Binding Mode (Type V)[1]

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, lenvatinib was found to possess a new Type V binding mode of kinase inhibition that is distinct from existing compounds. In addition, lenvatinib 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.

3. About Renal Cell Carcinoma

Renal cell carcinoma is the most common form of cancer to affect the kidneys. The incidence of renal cell carcinoma in people aged in their late 50s is rising, and is more likely to affect men than women. The number of patients with renal cancer (including renal cell carcinoma and renal pelvic 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]. While the standard treatment method primarily consists of surgery, once the cancer has metastasized or relapsed, the main treatment method becomes chemotherapy using molecular targeted drugs.

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

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