

PHASE II TRIAL OF ANTICANCER AGENT LENVATINIB IN RENAL CELL CARCINOMA MEETS PRIMARY ENDPOINT

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the Phase II part of a Phase I/II clinical trial (Study 205) of its in-house developed anticancer agent lenvatinib mesylate (lenvatinib) in unresectable advanced or metastatic renal cell carcinoma has met its primary endpoint.

The second part of Study 205 was an open-label, multicenter study of lenvatinib alone, and in combination with the anticancer agent everolimus, in patients with unresectable advanced or 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 receive either lenvatinib (18 mg) plus everolimus (5 mg), lenvatinib alone (24 mg), or everolimus alone (10 mg) to compare the safety and efficacy of these three regimens.

From the preliminary results of the study, both lenvatinib plus everolimus and the lenvatinib alone groups prolonged progression free survival (PFS), the study's primary endpoint, compared to everolimus alone, and the lenvatinib plus everolimus group in particular showed a highly statistically significant improvement. The most common treatment-related adverse events reported in the lenvatinib plus everolimus group were diarrhea, decreased appetite, fatigue, nausea, and hypertension, and in the lenvatinib alone group were diarrhea, nausea, decreased appetite, hypertension, fatigue, and vomiting. Detailed results of the study will be presented at an academic conference in the near future.

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. 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 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. Eisai will share these study results with regulatory authorities to discuss further steps.

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. It is the first compound that has been confirmed through X-ray crystal structural analysis to possess a novel binding mode (Type V) to VEGFR2¹. Furthermore, lenvatinib exhibits rapid and potent inhibition of kinase activity, according to kinetic analysis¹. Currently, Eisai has already submitted regulatory applications for lenvatinib seeking indication approval for thyroid cancer to health authorities firstly in Japan, the United States and the EU, and is filing subsequent applications in other countries worldwide. Eisai has also initiated a global Phase III trial of lenvatinib in hepatocellular carcinoma and Phase II studies of lenvatinib in several other tumor types 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 (E7080)

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)), 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. Lenvatinib exhibits rapid and potent inhibition of kinase activity¹, simultaneously inhibiting the activity of VEGFR, FGFR and also RET which are especially involved in tumor angiogenesis and proliferation of thyroid cancer, and has been confirmed to possess a novel binding mode (Type V)¹. Eisai has already submitted regulatory applications for lenvatinib seeking indication approval for thyroid cancer to health authorities firstly in Japan in June 2014, followed by the United States, the EU, Switzerland, South Korea, Canada, Singapore and Russia. 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 Europe². 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/Default.aspx>