

**EISAI TO INITIATE PHASE III CLINICAL STUDY OF
ANTICANCER AGENT LENVATINIB AS POTENTIAL FIRST-LINE THERAPY
FOR ADVANCED RENAL CELL CARCINOMA**
*SIMULTANEOUS DEVELOPMENT OF TWO COMBINATION THERAPIES
LENVATINIB/EVEROLIMUS AND LENVATINIB/PEMBROLIZUMAB*

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today the initiation of a global Phase III Clinical Study (Study 307, CLEAR Study) of its in-house developed multiple receptor tyrosine kinase inhibitor lenvatinib mesylate (lenvatinib) in respective combination regimens with the anticancer agent everolimus and the anti-PD-1 antibody pembrolizumab as a potential first-line treatment for advanced renal cell carcinoma.

The CLEAR (Comparison of the efficacy and safety of Lenvatinib in combination with Everolimus or pembrolizumab versus sunitinib alone in first-line treatment of subjects with Advanced Renal cell carcinoma) study is a multicenter, randomized, open-label Phase III clinical study to compare the efficacy and safety of lenvatinib/everolimus and lenvatinib/pembrolizumab versus sunitinib alone in first-line treatment in patients with advanced renal cell carcinoma. The primary outcome measure will be progression-free survival.

Non-clinical research into the combination of lenvatinib and everolimus suggested synergistic enhancement of antiangiogenic activity and a stronger antitumor effect than either monotherapy in renal cell carcinoma models through the respective inhibition of signaling pathways which facilitate tumor angiogenesis, upstream (vascular endothelial growth factor receptor [VEGFR] and fibroblast growth factor receptor [FGFR]) with lenvatinib and downstream (mammalian target of rapamycin [mTOR]) with everolimus.^{1,2} Furthermore, non-clinical research into the combination of lenvatinib and anti-PD-1 antibody suggested that the combination has a mechanism of action in which lenvatinib enhances the antitumor activity of the anti-PD-1 antibody by reducing immunosuppressive cells.³

The number of patients with renal cancer is estimated to be approximately 338,000 worldwide, including approximately 115,000 in Europe, 58,000 in the United States and 17,000 in Japan.⁴ Renal cell carcinoma comprises more than 90% of all malignancies of the kidney,⁵ and occurs when malignant cells are found in the lining of the tubules of the kidney. The incidence of renal cell carcinoma in people over 55 years of age is rising, and it 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 is molecular targeted drug therapy, however with low 5-year survival rates, this remains a disease with significant unmet medical need.

Currently lenvatinib has been approved in over 45 countries including the United States, Japan and in Europe as a treatment for refractory thyroid cancer. In May 2016, lenvatinib was approved in combination with everolimus for the treatment of patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy by the U.S. Food and Drug Administration in the United States. Furthermore, lenvatinib was approved in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma following one prior vascular endothelial growth factor targeted therapy in Europe in August 2016.

Eisai regards oncology as a key therapeutic area and is aiming to discover revolutionary new medicines with the potential to cure cancer. Eisai remains committed to providing further clinical evidence for lenvatinib aimed at maximizing value of the drug as it seeks to contribute further to addressing the diverse needs of, and increasing the benefits provided to, patients with cancer, their families, and healthcare providers.

*Please refer to the following notes for the approved indications of lenvatinib in the United States, Japan and Europe

Media Inquiries:
Public Relations Department,
Eisai Co., Ltd.
+81-(0)3-3817-5120

[Notes to editors]

1. About lenvatinib mesylate (“lenvatinib”, generic name, product names: Lenvima[®], Kisplyx[®])

Discovered and developed in-house, 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.

Currently, Eisai has obtained approval for lenvatinib as a treatment for refractory thyroid cancer in over 45 countries including in the United States, Japan, in Europe, Korea, Canada, and Mexico, and is undergoing regulatory review in countries throughout the world including South Africa and Malaysia. Specifically, Eisai has obtained approval for the agent indicated in the United States for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, in Japan for the treatment of unresectable thyroid cancer, and in Europe for the treatment of adult patients with progressive, locally advanced or metastatic differentiated (papillary, follicular, Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine, respectively.

Lenvatinib was also approved in the United States in May 2016 for an additional indication in combination with everolimus for the treatment of patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy. Furthermore, lenvatinib was approved in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF) targeted therapy in Europe in August 2016. Lenvatinib will be launched in Europe under the brand name Kisplyx[®] for this indication.

Meanwhile, Eisai is conducting clinical studies of lenvatinib in several other tumor types such as hepatocellular carcinoma (Phase III), endometrial carcinoma (Phase II), biliary tract cancer (Phase II), and in combination with pembrolizumab for various types of cancer (Phase Ib/II).

2. About the Phase III Clinical Study (Study 307, CLEAR Study)

CLEAR Study is a global, multicenter, randomized, open-label, Phase III clinical study to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma. The study will be initially conducted in the United States and Europe, and Eisai is currently considering adding Japan to the study in the future. Approximately 735 patients aged 18 years or older with histological or cytological confirmation of advanced renal cell carcinoma with a clear-cell component and Karnofsky Performance Status⁶ of 70 or greater are randomized 1:1:1 to one of three treatment arms to receive either lenvatinib 18 mg (orally, once daily) plus everolimus 5 mg (orally, once daily) [arm A], lenvatinib 20 mg (orally, once daily) plus pembrolizumab 200 mg (intravenously every three weeks) [arm B], or sunitinib 50 mg (orally, once daily) on a schedule of four weeks on treatment followed by two weeks off [arm C]. The primary outcome is to compare progression-free survival between the arm A versus arm C, and the arm B versus arm C. Secondary outcomes are objective response rate, overall survival, and safety.

3. About Non-clinical Research into lenvatinib in Combination with everolimus^{1,2}

It is known that lenvatinib inhibits VEGFR and FGFR which are upstream RTK signaling pathways, and that everolimus suppresses the protein mTOR (mammalian target of rapamycin) found downstream of these signaling pathways. In vitro and animal models have suggested that the combination of lenvatinib and everolimus suppresses RTK signaling pathways, which facilitate tumor angiogenesis, at two points both upstream and down, enabling synergistic signaling inhibition for enhanced antiangiogenesis in vitro. The combination demonstrated stronger antitumor activity than either monotherapy in the in vivo animal model using A498 and Caki-1 human renal cell carcinoma xenograft models.

4. About Non-clinical Research into lenvatinib in Combination with Anti-PD-1 Antibody³

Animal models have shown that lenvatinib activates tumor immunity via the modulation of tumor associated macrophages. Tumor associated macrophages have been reported as a negative regulator of cytotoxic T-cells and a promoter of tumor cell metastasis. Animal models suggest that when lenvatinib is combined with an anti-PD-1 antibody, lenvatinib enhances antitumor activity of the anti-PD-1 antibody by suppressing tumor associated macrophages.

- 1 Mitsuhashi K., et al. Effects of lenvatinib mesilate in combination with everolimus on VEGF and FGF-driven angiogenesis and tumor growth, *Cancer Research* 76(14 Supplement):3262-3262 July 2016
- 2 Adachi Y., et al. Lenvatinib in combination with everolimus demonstrated enhanced antiangiogenesis and antitumor activity in human RCC xenograft models, *Cancer Research* 76(14 Supplement):3264-3264 July 2016
- 3 Kato Y., Effects of lenvatinib on tumor-associated macrophages enhance antitumor activity of PD-1 signal Inhibitors, *Mol Cancer Ther* 2015;14(12 Suppl 2):Abstract nr A92
- 4 Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, <http://globocan.iarc.fr/>
- 5 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).
- 6 The Karnofsky Performance Score is a standardized method to measure a cancer patient's ability to carry out daily activities and is classified into 11 stages. A score of 100 represents normal function with no evidence of disease. The greater the functional impairment, the lower the score.