

EISAI PRESENTS RESULTS OF PHASE Ib/II CLINICAL STUDY OF LENVIMA® (LENVATINIB) IN COMBINATION WITH PEMBROLIZUMAB FOR RENAL CELL CARCINOMA IN ORAL SESSION AT ESMO 2017 CONGRESS

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, “Eisai”) announced today that an oral presentation on the results of the renal cell carcinoma cohort from a Phase Ib/II clinical study of its in-house discovered and developed multiple receptor tyrosine kinase inhibitor lenvatinib mesylate (product names: Lenvima® / Kisplyx®, “lenvatinib”) in combination with the Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside of the United States and Canada) anti-PD-1 therapy pembrolizumab (product name: KEYTRUDA®) developed by was given at the European Society for Medical Oncology (ESMO) 2017 Congress¹, which took place in Madrid, Spain. This combination therapy is being jointly developed by both companies.

The presentation at the ESMO 2017 Congress highlighted an analysis of 30 patients with metastatic renal cell carcinoma enrolled in combined Phase Ib and Phase II parts as of March 1, 2017. Based on the results of the analysis (investigator review), the primary endpoint of the Phase II part, Objective Response Rate* at 24 weeks after treatment began (ORR_{Week24}) was 63%, with tumor regression observed in 93% (n = 28) of patients since beginning treatment (baseline). A tumor response was observed regardless of whether patients had previously received treatment or not (see table below).

Primary Endpoint	All 30 patients	No treatment history (n = 12)	Previously treated (n = 18)
ORR _{Week24} , Investigator review	63% (n = 19)	83% (n = 10)	50% (n = 9)
95% Confidence Interval	44-80	52-98	26-74

Additionally, tumor response was observed regardless of whether PD-L1 was expressed or not. In this study, the most frequently observed adverse events (top 6) were diarrhea, fatigue, hypothyroidism, stomatitis, hypertension and nausea.

In 2012, 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.² Renal cell carcinoma comprises more than 90% of all malignancies of the kidney,³ and originates from malignant cells 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.

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 this combination therapy aimed at earlier submission for renal cell carcinoma 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.

*Objective Response Rate: The ratio of patients whose tumor size decreased by at least 30% (Partial Response) or disappeared (Complete Response) after treatment.

KEYTRUDA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Kenilworth, NJ, USA.

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

[Notes to editors]

1. About lenvatinib mesylate (product names: Lenvima, Kisplyx, “lenvatinib”)

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 50 countries, including the United States, Japan, and in Europe. Additionally, Eisai has obtained approval for the agent in combination with everolimus as a treatment for renal cell carcinoma (second-line) in over 35 countries, including the United States and in Europe. In Europe, the agent was launched under the brand name Kisplyx for renal cell carcinoma.

Furthermore, in a Phase III clinical study (Study 304) comparing safety and efficacy of the agent versus sorafenib for the treatment of hepatocellular carcinoma, the agent achieved its primary endpoint of overall survival, meeting the statistical criteria for non-inferiority to sorafenib. Following the submission of applications in Japan (June 2017), the United States and Europe (July 2017), Eisai also plans to submit an application for lenvatinib for the treatment of hepatocellular carcinoma in China within the latter half of fiscal 2017.

Additionally, a Phase III clinical study (Study 307) of the agent in combination with either everolimus or pembrolizumab as a first line treatment for renal cell carcinoma is underway.

2. About Study 111

Study 111 is a multicenter, open-label Phase Ib/II clinical study being carried out in the United States to evaluate the efficacy and safety of lenvatinib in combination with pembrolizumab. The primary endpoint of the Phase Ib part was to determine the maximum tolerated dose. Thirteen patients with unresectable solid tumors (non-small cell lung cancer, renal cell carcinoma, endometrial cancer, urothelial cancer, head and neck cancer, and melanoma) who had progressed after treatment with approved therapies or for which there are no standard effective therapies available were administered 24 mg (3 patients) or 20 mg (10 patients) of lenvatinib orally daily, as well as 200 mg of pembrolizumab intravenously every three weeks. The Phase II part was conducted on patients with select solid tumors who had previously undergone less than 2 chemotherapy regimens, with a recommended dosage of 20 mg of lenvatinib daily and 200 mg of pembrolizumab every three weeks as determined based on the results of the Phase Ib part. The primary endpoint of the Phase II part was objective response rate at 24 weeks after treatment began, with secondary endpoints including objective response rate, disease control rate, progression-free survival, and duration of response. Currently, the Phase II part is underway, with enrollment expanded for the endometrial cancer cohort.

In addition, Phase Ib clinical studies of lenvatinib in combination with pembrolizumab for the treatment of select solid tumors (Study 115) and hepatocellular carcinoma (Study 116) are ongoing in Japan.

3. About research on mechanisms of action in combination of lenvatinib and anti-PD-1 antibody

In a non-clinical study where mouse models were inoculated with mouse liver cancer, melanoma or colon cancer cell lines and treated with a combination of lenvatinib with an anti-mouse PD-1 antibody, synergistic anti-tumor activities were demonstrated.⁴ These are thought to be a result of an immunostimulatory response through a reduction in immunosuppressive tumor-associated macrophages and an increase in cytotoxic T lymphocytes by lenvatinib.

¹ Lee CH, et al. A Phase 1b/2 Trial of Lenvatinib + Pembrolizumab in Patients With Renal Cell Carcinoma. *ESMO Congress Abstract*, 2017; #8470

² GLOBOCAN2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. <http://globocan.iarc.fr/>

³ Eble J.N, et al. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs, *World Health Organisation classification of tumours*. (International Agency for Research on Cancer, Lyon, France in 2004)

⁴ Kato Y, et al. Upregulation of memory T cell population and enhancement of Th1 response by lenvatinib potentiate anti-tumor activity of PD-1 signaling blockade : Lenvatineb and PD-1 mAb combination. *AACR Meeting Abstract*, 2017; #4614