

PHASE III TRIAL RESULTS OF ANTICANCER AGENT LENVATINIB IN HEPATOCELLULAR CARCINOMA PUBLISHED IN THE LANCET

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the results of a Phase III study (REFLECT study, Study 304) of its in-house discovered and developed anticancer agent lenvatinib mesylate (product names: Lenvima® / Kispalyx®, "lenvatinib") in patients with hepatocellular carcinoma (HCC) have been published in the online version of *The Lancet*,¹ which is one of the world's most prestigious medical journals and was recently ranked second in the world in terms of Impact Factor. (Lead author: Professor and Chairman Masatoshi Kudo of Kindai University Faculty of Medicine, Title of paper: "Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial")

The REFLECT study reported on in the paper was a multicenter, open-label, randomized, global Phase III study comparing the efficacy and safety of lenvatinib versus sorafenib, a standard treatment for advanced hepatocellular carcinoma, as a first-line treatment in patients with unresectable HCC. In this study, lenvatinib demonstrated a treatment effect on the primary endpoint of Overall Survival (OS) by statistical confirmation of non-inferiority to sorafenib. Additionally, lenvatinib showed highly statistically significant and clinically meaningful improvements in the secondary endpoints of Progression Free Survival (PFS), Time To Progression (TTP), and Objective Response Rate (ORR).

The paper also reported on the results of an exploratory analysis of the secondary endpoints based on blinded independent imaging review (IIR). The IIR based on both RECIST1.1, which uses the traditional assessment of the effect on change in tumor diameter, and mRECIST, which takes into account areas of tumor necrosis in addition to the RECIST 1.1 criteria, confirmed similar findings to the investigators' review (per mRECIST criteria) of extensions in PFS and TTP as well as an increase in ORR compared to sorafenib based on lenvatinib's superior reduction in tumor size.

In this study, the five most common adverse events observed in the lenvatinib arm were hypertension, diarrhea, decreased appetite, weight loss and fatigue, which is consistent with the known safety profile of lenvatinib.

Eisai has submitted applications for lenvatinib for the treatment of HCC in Japan (June 2017), the United States and Europe (July 2017), China (October 2017), Taiwan (December 2017) and other countries. Eisai remains committed to providing additional clinical evidence for lenvatinib aimed at maximizing the value of the drug to patients 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.

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[Notes to editors]

1. About lenvatinib mesylate (generic name, “lenvatinib”, product name: Lenvima / Kispplx)

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, in Europe and Asia, under the brand name Lenvima. Additionally, Eisai has obtained approval for lenvatinib in combination with everolimus as a treatment for renal cell carcinoma (second-line) in over 40 countries, including the United States and in Europe. In Europe, the agent was launched under the brand name Kispplx for renal cell carcinoma.

A Phase III study of lenvatinib in separate combinations with everolimus and pembrolizumab in renal cell carcinoma (first-line) is underway. A Phase Ib/II study to investigate lenvatinib in combination with pembrolizumab in select solid tumors (endometrial cancer, non-small cell lung cancer, renal cell carcinoma, urothelial cancer, head and neck cancer, and melanoma) and a Phase Ib study in HCC are also underway. Additionally, a Phase Ib study to investigate lenvatinib in combination with nivolumab in HCC has been initiated in Japan.

2. About the REFLECT Study (Study 304) ¹

The REFLECT study is a multicenter, open-label, randomized, global Phase III study comparing the efficacy and safety of lenvatinib versus sorafenib, a standard treatment for advanced hepatocellular carcinoma (HCC), as a first-line treatment for patients with unresectable HCC. In the study, 954 patients were randomized in a 1:1 ratio to receive lenvatinib 12 mg (≥ 60 kg) or 8 mg (< 60 kg) once a day, depending on baseline body weight (n= 478) or sorafenib 400 mg twice a day (n= 476). Treatment was continued until disease progression or unacceptable toxicity.

The primary endpoint of the study was OS, with the goal of demonstrating non-inferiority. Other factors including PFS, TTP, ORR and Quality of Life (QOL) were assessed as secondary endpoints.

In this study, the five most common adverse events observed in the lenvatinib arm were hypertension, diarrhea, decreased appetite, weight loss and fatigue, which is consistent with the known safety profile of lenvatinib.

3. About RECIST (Response Evaluation Criteria In Solid Tumors)

RECIST1.1 is a set of assessment criteria used to evaluate effects on solid cancers (based on changes in tumor diameter). mRECIST is a new criteria that takes into account areas of tumor necrosis in addition to RECIST1.1.

4. About Hepatocellular Carcinoma (HCC)

Liver cancer is the second-leading cause of cancer death, estimated to be responsible for 750,000 deaths per year globally. Additionally, 780,000 cases are newly diagnosed each year. ² There is a large regional difference, with about 80% of new cases occurring in Asian regions, including China and Japan. HCC accounts for 85% to 90% of liver cancer. Currently, systemic therapies approved for firstline treatment of HCC are limited, underscoring a great unmet medical need.

5. About *The Lancet*

First published in 1823 and with a history spanning over 190 years, *The Lancet* is an influential medical journal that is highly regarded worldwide.

Impact Factor is based on “2016 Journal Citation Reports[®], Clarivate Analytics 2017.”

¹ M Kudo, et al. “Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial” *The Lancet*, 2018

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