

**EISAI PRESENTS RESULTS OF ANALYSIS OF PHASE III TRIAL OF
LENVIMA® (LENVATINIB) IN HEPATOCELLULAR CARCINOMA
BASED ON INDEPENDENT IMAGING REVIEW AT ASCO-GI**

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that the results of an analysis of a Phase III trial (REFLECT study / Study 304)¹ of its in-house discovered and developed anticancer agent lenvatinib mesylate (product names: Lenvima® / Kisplyx®, "lenvatinib") versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma based on independent imaging review were presented² during the American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO-GI) 2018, in San Francisco, the United States.

The presentation reported on an exploratory analysis of the secondary endpoints of Progression Free Survival (PFS), Time To Progression (TTP), and Objective Response Rate (ORR) in the REFLECT study based on blinded independent imaging review (IIR).

The IIR based on both RECIST (Response Evaluation Criteria in Solid Tumors) 1.1, which uses the traditional assessment of the effect on change in tumor diameter, and modified RECIST (mRECIST), which takes into account areas of tumor necrosis in addition to the RECIST 1.1 criteria, confirmed the investigators' findings of extensions in PFS and TTP as well as an increase in ORR compared to sorafenib (refer to the tables below) based on lenvatinib's superior reduction in tumor size. The results of the blinded IIR of the REFLECT study support the imaging findings of the clinical trial investigators.

Efficacy Outcome	Assessment Method	Criteria	Lenvatinib 478 patients, Months (Median value)	Sorafenib 476 patients, Months (Median value)	Hazard Ratio (95% Confidence Interval)	P-value
PFS	Investigator	mRECIST	7.4	3.7	0.66 (0.57-0.77)	<0.00001
	IIR	mRECIST	7.3	3.6	0.64 (0.55-0.75)	<0.00001 (nominal)
		RECIST1.1	7.3	3.6	0.65 (0.56-0.77)	<0.00001 (nominal)
TTP	Investigator	mRECIST	8.9	3.7	0.63 (0.53-0.73)	<0.00001
	IIR	mRECIST	7.4	3.7	0.60 (0.51-0.71)	<0.00001 (nominal)
		RECIST1.1	7.4	3.7	0.61 (0.51-0.72)	<0.00001 (nominal)

Efficacy Outcome	Assessment Method	Criteria	Lenvatinib 478 patients, %	Sorafenib 476 patients, %	Odds Ratio (95% Confidence Interval)	P-value
ORR	Investigator	mRECIST	24.1	9.2	3.13 (2.15-4.56)	<0.00001
	IIR	mRECIST	40.6	12.4	5.01 (3.59-7.01)	<0.00001 (nominal)
		RECIST1.1	18.8	6.5	3.34 (2.17-5.14)	<0.00001 (nominal)

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.

Liver cancer is the second leading cause of cancer related deaths and is estimated to be responsible for 750,000 deaths per year globally. Additionally, 780,000 cases are newly diagnosed each year, about 80% of which occur in Asian regions, including Japan and China.³ Hepatocellular carcinoma accounts for 85% to 90% of primary liver cancer cases. Early stage hepatocellular carcinoma is treatable by a wide variety of means, including surgery, radiofrequency ablation, ethanol injection, and chemoembolization therapy, but treatment opinions for unresectable hepatocellular carcinoma are limited and the prognosis is very poor, meaning that this is an area of high unmet medical need.

Eisai submitted applications for an additional indication 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 generating scientific evidence aimed at maximizing the value of lenvatinib 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 / 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 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 in the United States, Europe, and other countries, as a treatment for renal cell carcinoma (second-line). In Europe, lenvatinib was launched under the brand name Kisplyx[®] for this indication.

A Phase III study (Study 307) of lenvatinib in separate combinations with everolimus and pembrolizumab in renal cell carcinoma (first-line) is underway. A Phase Ib/II study to investigate the agent in combination with pembrolizumab in select solid tumors (non-small cell lung cancer, renal cell carcinoma, endometrial cancer, urothelial cancer, head and neck cancer, and melanoma) is underway. Additionally, a Phase Ib study of the agent in hepatocellular carcinoma is also underway.

2. About Study 304

Study 304 is a multicenter, randomized, open-label, 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 for patients with unresectable hepatocellular carcinoma. In the study, 954 patients were randomized in a 1:1 ratio to receive lenvatinib 12 mg or 8 mg 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 Overall Survival (OS), with the goal of demonstrating non-inferiority. Other factors including PSF, 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 side-effect profile of lenvatinib.

3. About the Independent Imaging Review and the Clinical Trial Investigators' Review

In order to preserve the uniformity of imaging assessment, an independent imaging review is conducted by a testing organization (central testing laboratory) which is independent of the medical organizations conducting the clinical trial. The clinical trial investigators' review is a review by the physician in charge of the clinical trial at each medical

organization according to specific criteria (such as RECIST).

4. 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.

5. About Progression Free Survival (PFS), Time to Progression (TTP) and Objective Response Rate (ORR)

PFS is the time from the date of randomization to the date of disease progression, or date of death from any cause, whichever occurs first. TTP is the time until the date of disease progression, and is different to PFS in that it does not consider death from any cause. ORR is the combined proportion of patients whose tumor was eliminated (complete response) and whose tumor was reduced by over 30% in size (partial response).

- ¹ A. Cheng et al. "Phase 3 trial of lenvatinib vs sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma", the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO), (June 2017), Abstract No: 4001
- ² Lencioni R, et al. "Independent imaging review (IIR) results in a phase 3 trial of lenvatinib (LEN) versus sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC)," ASCO-GI 2018, Abstract #345
- ³ GLOBOCAN2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. <http://globocan.iarc.fr/>