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Eisai Co., Ltd.

EISAI PRESENTS RESULTS OF PHASE III CLINICAL STUDY OF LENVIMA® (LENVATINIB) IN UNRESECTABLE HEPATOCELLULAR CARCINOMA AT 11TH ILCA ANNUAL CONFERENCE

RESULTS OF SUBPOPULATION ANALYSIS OF PATIENTS WITH HEPATITIS B VIRUS COINFECTION

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") has announced that the results of a subpopulation analysis of patients with hepatitis B virus (HBV) coinfection in a Phase III trial (REFLECT / Study 304) [1] of its in-house discovered and developed anticancer agent lenvatinib mesylate (product names: Lenvima® / Kisplyx®, "lenvatinib") versus sorafenib as a first-line treatment for unresectable HCC were presented for the first time during the 11th Annual Conference of the International Liver Cancer Association (ILCA) held in Seoul, South Korea.

In the total population analysis of this study, the treatment effect of lenvatinib for all patients on the primary endpoint of Overall Survival (OS) was demonstrated by statistical confirmation of non-inferiority to sorafenib. 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 analysis results presented at ILCA indicate that in comparison to the total population, lenvatinib demonstrated a lower hazard ratio for OS, FPS, and TTP, and a higher odds ratio for ORR in the subpopulation of patients with HBV (See table below). HBV is considered to be a negative predictor of tumor response to existing drug therapies, so lenvatinib, which demonstrated a therapeutic effect in patients with HBV, is expected to be a new treatment option for patients with HCC.

Efficacy outcome Median (95% CI)	Total Population		Patients with HBV	
	Lenvatinib (n = 478)	Sorafenib (n = 476)	Lenvatinib (n = 259)	Sorafenib (n = 244)
OS, months	13.6 (12.1–14.9)	12.3 (10.4–13.9)	13.4 (11.6–14.6)	10.2 (8.6–12.4)
HR(95% CI)	0.92 (0.79–1.06)		0.83 (0.68–1.02)	
PFS, months	7.4 (6.9–8.8)	3.7 (3.6–4.6)	7.3 (5.6–9.1)	3.6 (2.6–3.6)
HR(95% CI)	0.66 (0.57–0.77)		0.62 (0.50–0.75)	
TTP, months	8.9 (7.4–9.2)	3.7 (3.6–5.4)	7.6 (6.6–9.2)	3.6 (3.4–3.7)
HR(95% CI)	0.63 (0.53–0.73)		0.58 (0.47–0.72)	
ORR, %	24.1 (20.2–27.9)	9.2 (6.6–11.8)	20.8 (15.9–25.8)	8.2 (4.8–11.6)
Odds Ratio(95% CI)	3.13 (2.15–4.56)		3.15 (1.80–5.53)	

** CI: Confidence Interval, HR: Hazard Ratio, OR: Odds Ratio*

Additionally, safety results were similar in patients with HBV and the total population in the lenvatinib arm. The five most common treatment-emergent adverse events in patients with HBV in the lenvatinib arm were hypertension, diarrhea, decreased weight, fatigue and decreased appetite.

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.[2] HCC accounts for 85% to 90% of primary liver cancer cases. Treatment options for unresectable HCC are limited and the prognosis is very poor, making this an area of high unmet medical need.
Following submissions in Japan (June 2017), the United States, and Europe (July 2017), Eisai will submit a regulatory application for lenvatinib in HCC in China within the latter half of fiscal 2017.

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 (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 PDGFRα; 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, and in Europe. 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 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 REFLECT Study (Study 304)[1]

The REFLECT study (A Multicenter, Randomized, Open-Label, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma) is a multicenter, open-label, randomized, global Phase III study comparing the efficacy and safety of lenvatinib versus sorafenib. 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 Overall Survival (OS), with the goal of demonstrating non-inferiority. Other factors including Progression Free Survival (PFS), Time To Progression (TTP), Objective Response Rate (ORR) and Quality of Life (QOL) were assessed as secondary endpoints.

According to the results of the study, lenvatinib met the statistical criteria for non-inferiority in the primary endpoint of OS compared to sorafenib (lenvatinib 13.6 months versus sorafenib 12.3 months in median, Hazard Ratio [HR] 0.92, 95% Confidence Interval [CI] = 0.79-1.06)

Additionally, lenvatinib showed statistically significant improvements in the three secondary efficacy endpoints, doubling sorafenib's median values and ratios: PFS (lenvatinib 7.4 months versus sorafenib 3.7 months in median, HR 0.66, 95% CI = 0.57-0.77, P<0.00001), TTP (lenvatinib 8.9 months versus sorafenib 3.7 months in median, HR 0.63, 95% CI = 0.53-0.73, P<0.00001) and ORR (lenvatinib 24% versus sorafenib 9%, P<0.00001).

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.

[1] Cheng A 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] GLOBOCAN2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/