No. 17-54

September 27, 2017
Eisai Co., Ltd.

APPLICATION FOR ADDITIONAL INDICATION OF LENVIMA® FOR HEPATOCELLULAR CARCINOMA ACCEPTED FOR REVIEW BY U.S. FDA

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") has announced that the application submitted for an additional indication of its in-house discovered and developed anticancer agent Lenvima® (generic name: lenvatinib mesylate) for the treatment of hepatocellular carcinoma (HCC) has been accepted for review by the U.S. Food and Drug Administration (FDA). Lenvatinib for the treatment of HCC is designated as an orphan drug by the FDA.

This application is based on the results of the REFLECT study (Study 304), a multicenter, open-label, randomized, global Phase III trial comparing the efficacy and safety of Lenvima versus sorafenib, a standard treatment for HCC, as a first-line treatment for patients with unresectable HCC.[1]

In the REFLECT study, Lenvima met the primary endpoint and demonstrated an overall survival (OS) treatment effect by the statistical confirmation of non-inferiority compared to sorafenib. Developing first-line treatments for HCC is challenging, and over the past 10 years, four previous first-line Phase III studies investigating other agents compared to sorafenib have failed to achieve their endpoints in OS.[2]
Additionally, Lenvima 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). In this study, the five most common adverse events observed in the Lenvima arm were hypertension, diarrhea, decreased appetite, weight loss and fatigue, which is consistent with the known side-effect profile of Lenvima.

Liver cancer is the second leading cause of cancer related death and is estimated to be responsible for 750,000 deaths per year globally (27,000 per year in the US), with 780,000 cases newly diagnosed each year (30,000 per year in the US).[3] HCC accounts for 85% to 90% of 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.

Eisai positions oncology as a key therapeutic area, and is aiming to discover revolutionary new medicines with the potential to cure cancer. Eisai is committed to exploring the potential clinical benefits of Lenvima 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 Lenvima (generic name: lenvatinib mesylate)

Discovered and developed in-house, Lenvima 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 Lenvima 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 (RCC) (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 RCC.

A Phase III study of Lenvima in separate combinations with everolimus and pembrolizumab in RCC (first-line) was initiated and is underway. A Phase Ib/II study to investigate the agent in combination with pembrolizumab in select solid tumors (endometrial cancer, non-small cell lung cancer, RCC, urothelial cancer, head and neck cancer, and melanoma) and a Phase Ib study in HCC are also underway.

Following the submission of applications in Japan (June 2017), the United States and Europe (July 2017), Eisai also plans to submit an application for Lenvima for the treatment of HCC in China within the latter half of fiscal 2017.

2. About the 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 Lenvima versus sorafenib. In the study, 954 patients were randomized in a 1:1 ratio to receive Lenvima 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 PFS, TTP, ORR and Quality of Life (QOL) were assessed as secondary endpoints.

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

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

Furthermore, EORTC QLQ-C30 and QLQ-HCC18 questionnaires were used to evaluate overall QOL. In both groups, scores decreased after the administration of the agents. However, within 3 categories in EORTC QLQ-C30 (role functioning, pain, diarrhea) and two categories in QLQ-HCC18 (nutrition, body image), it was found that Lenvima helped to delay deterioration of QOL compared to sorafenib (nominal P-value < 0.01).

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

3. About Hepatocellular Carcinoma (HCC)

Liver cancer is the second leading cause of cancer related death, and is estimated to be responsible for 750,000 deaths per year globally. Additionally, 780,000 cases are newly diagnosed each year.[3] 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. HCC is associated with chronic liver disease, in particular cirrhosis. Major causes of cirrhosis include hepatitis B virus and hepatitis C virus. However, according to a recent investigation, non-B/non-C HCC is on the rise. Surgery is the first option for treatment, but for patients with unresectable HCC who are not amenable for potentially curative therapeutic interventions, which include liver transplant, surgical resection, and tumor ablation (typically radiofrequency ablation or cryotherapy), or who are not suitable for transarterial chemoembolization (TACE), treatment options are limited and the prognosis is very poor. Currently, sorafenib is the only approved systemic therapy for frontline treatment of these patients, underscoring a great unmet medical need.

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 Llovet JM and Hernandez-Gea V. Hepatocellular carcinoma: Reasons for Phase III failure and novel perspectives on trial design. *Clin Cancer Res.* 2014;20(8):2072-2079.

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