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Eisai Co., Ltd.

LENVIMA® (lenvatinib) in Combination with Pembrolizumab and Transarterial Chemoembolization (TACE) Approved in China for the Treatment of Unresectable, Non-Metastatic Hepatocellular Carcinoma

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that its in-house discovered tyrosine kinase inhibitor, "LENVIMA®" (generic name: lenvatinib mesylate), in combination with the anti-PD-1 antibody, pembrolizumab, and transarterial chemoembolization (TACE) has been approved by the National Medical Products Administration (NMPA) of China for unresectable, non-metastatic hepatocellular carcinoma.

This approval is based on interim analysis results from the pivotal Phase III LEAP-012 trial. The results of this trial were presented at the European Society for Medical Oncology (ESMO) Annual Congress 2024 held in September 2024[1] and published in *The Lancet* in January 2025.[2] In this trial, LENVIMA in combination with pembrolizumab and TACE (the "combination therapy") demonstrated a statistically significant and clinically meaningful improvement in one of the trial's primary endpoints, progression-free survival (PFS), reducing the risk of disease progression or death by 34% (Hazard Ratio [HR]=0.66 [95% Confidence Interval (CI), 0.51-0.84]; p=0.0002) compared to TACE alone*.[2] Median PFS was 14.6 months (95% CI, 12.6-16.7) in the combination therapy and 10.0 months (95% CI, 8.1-12.2) in TACE alone.[2] At this analysis, a trend toward improvement in overall survival (OS), the trial's other primary endpoint, was observed for the combination therapy versus TACE alone (HR=0.80 [95% CI, 0.57-1.11]; p=0.087).[2]

237 patients received the combination therapy and 241 patients received TACE alone.[2] Treatment-Emergent Adverse Events (TEAEs) occurred in 99.6% (n=236) of patients receiving the combination therapy versus 96.7% (n=233) of patients receiving TACE alone and led to the discontinuation of both study drugs in 13.1% (n=31) versus 4.1% (n=10) of patients, respectively.[2] Grade 3, 4, or 5 TEAEs occurred in 82.3% (n=195) of patients receiving the combination therapy versus 47.7% (n=115) for TACE alone and TEAEs led to death in 4.2% (n=10) versus 2.5% (n=6) of patients, respectively.[2]

Liver cancer is one of the leading causes of cancer-related deaths worldwide.[3] In 2022, it was estimated there were more than 865,000 new cases globally and 367,000 in China, with more than 757,000 deaths worldwide, including 316,000 in China.[3,4] China is estimated to account for more than 40% of global new cases and deaths.[3,4] Hepatocellular carcinoma (HCC) is the most common type of liver cancer, representing approximately 90% of primary liver cancer cases.[5] TACE has been a standard of care for patients with unresectable, non-metastatic HCC for many years. However, since many patients experience disease progression within one year[6,7,8,9], new treatment options have been sought.

LENVIMA monotherapy has been approved for the treatment of patients with unresectable HCC in more than 80 countries, including in Japan, the U.S., Europe and China and has made contributions to many patients to date. With this approval, it is expected that LENVIMA will further expand its contribution to patients with hepatocellular carcinoma in China.

Eisai positions oncology as a key therapeutic area and is aiming to discover innovative new medicines with the potential to cure cancer. Eisai is committed to expanding the potential clinical benefits of lenvatinib for cancer treatment, as it seeks to contribute to addressing the diverse needs of, and increasing the benefits provided to, patients with cancer, their families and healthcare professionals.

In March 2018, Eisai and Merck & Co., Inc., Rahway, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of lenvatinib.

*TACE alone: In addition to TACE, oral placebo and intravenous placebo corresponding to LENVIMA and pembrolizumab were administered.

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[Notes to editors]

1. About LEAP-012

LEAP-012 is a multicenter, randomized, double-blind Phase 3 trial (ClinicalTrials.gov, NCT04246177) evaluating LENVIMA plus pembrolizumab in combination with TACE versus dual placebo plus TACE for the treatment of patients with unresectable, non-metastatic HCC. The primary endpoints are PFS as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) modified to follow a maximum of 10 target lesions, and with a requirement that new intrahepatic lesions must meet LI-RADS 5 criteria, and OS. Secondary endpoints include objective response rate, duration of response, disease control rate, and time to progression as assessed by BICR per above-mentioned RECIST v1.1 and Modified Response Evaluation Criteria in Solid Tumors (mRECIST), as well as PFS as assessed by BICR per mRECIST and safety. The study randomized 480 patients 1:1 to receive:

- LENVIMA (12 mg [for participants with screening body weight ≥60 kg] or 8 mg [for participants with screening body weight <60 kg] orally once a day) plus pembrolizumab (400 mg IV every six weeks [Q6W]) in combination with TACE (conducted as a background procedure of chemotherapeutic and embolic agents injected via hepatic artery 2-4 weeks after start of study intervention, and after the first tumor assessment scan and ≥1 month after the first TACE); or
- oral placebo administered once a day plus IV placebo administered Q6W in combination with TACE.

All study drugs were continued until protocol-specified discontinuation criteria. pembrolizumab was administered for up to two years (approximately 18 doses). After completing two years of combination therapy, LENVIMA may have been administered as a single agent until protocol-specified discontinuation criteria were met.

2. About LENVIMA (lenvatinib) Capsules

LENVIMA, discovered and developed by Eisai, is an orally available multiple receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). LENVIMA inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF)

receptors FGFR1-4, the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. In syngeneic mouse tumor models, LENVIMA decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone. LENVIMA has been approved for the indications below.

Thyroid cancer

• Indication as monotherapy

(Approved mainly in Japan, the United States, Europe, China and Asia)

Japan: Unresectable thyroid cancer

The United States: The treatment of patients with locally recurrent or metastatic, progressive, radioiodine-refractory differentiated thyroid cancer (DTC)

Europe: The treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)

Hepatocellular carcinoma

• Indication as monotherapy

(Approved mainly in Japan, the United States, Europe, China and Asia)

Japan: Unresectable hepatocellular carcinoma

The United States: The first-line treatment of patients with unresectable hepatocellular carcinoma (HCC)

Europe: The treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy

Thymic carcinoma

• Indication as monotherapy (Approved in Japan)

Japan: Unresectable thymic carcinoma

Renal cell carcinoma (In Europe other than the United Kingdom, the agent was launched under the brand name Kisplyx®)

• Indication in combination with everolimus

(Approved mainly in the United States, Europe and Asia)

The United States: The treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy

Europe: The treatment of adult patients with advanced renal cell carcinoma following one prior vascular endothelial growth factor (VEGF) targeted therapy

• Indication in combination with pembrolizumab

(Approved mainly in Japan, the United States, Europe and Asia)

Japan: Radically unresectable or metastatic renal cell carcinoma

The United States: The first-line treatment of adult patients with advanced renal cell carcinoma

Europe: The first-line treatment of adult patients with advanced renal cell carcinoma

Endometrial carcinoma

• Indication in combination with pembrolizumab

(Approved mainly in Japan, the United States, Europe and Asia)

Japan: Unresectable, advanced or recurrent endometrial carcinoma that progressed after cancer chemotherapy

The United States: The treatment of patients with advanced endometrial carcinoma (EC) that is not microsatellite

instability-high (MSI-H) or mismatch repair deficient (dMMR) who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation

Europe: The treatment of adult patients with advanced or recurrent endometrial carcinoma (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery

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