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LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) in Combination With Transarterial Chemoembolization (TACE) Significantly Improved Progression-Free Survival Compared to TACE Alone in Patients With Unresectable, Non-Metastatic Hepatocellular Carcinoma (HCC)

In the Phase 3 LEAP-012 trial, LENVIMA plus KEYTRUDA in combination with TACE reduced the risk of disease progression or death by 34% compared to TACE alone

Late-breaking first interim analysis results are being presented during a Presidential Symposium session at the European Society for Medical Oncology Congress 2024

TOKYO and RAHWAY, NJ, Sept. 17, 2024 – Eisai (Headquarters: Tokyo, CEO: Haruo Naito) and Merck & Co., Inc., Rahway, NJ, USA (known as MSD outside of the United States and Canada) today announced results from the first interim analysis of the Phase 3 LEAP-012 trial evaluating LENVIMA® (lenvatinib), the orally available multiple receptor tyrosine kinase inhibitor (TKI) discovered by Eisai, plus KEYTRUDA® (pembrolizumab), the anti-PD-1 therapy from Merck & Co., Inc., Rahway, NJ, USA, in combination with transarterial chemoembolization (TACE) compared to TACE alone for the treatment of patients with unresectable, non-metastatic hepatocellular carcinoma (HCC). These late-breaking data were presented for the first time on September 14 (Central European Summer Time) during a Presidential Symposium at the European Society for Medical Oncology (ESMO) Congress 2024 (Presentation #LBA3).

After a median follow-up of 25.6 months (range, 12.6-43.5), LENVIMA plus KEYTRUDA in combination with TACE demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS), reducing the risk of disease progression or death by 34% (HR=0.66 [95% CI, 0.51-0.84]; p=0.0002) compared to TACE alone. Median PFS was 14.6 months (95% CI, 12.6-16.7) for the LENVIMA plus KEYTRUDA-based regimen versus 10.0 months (95% CI, 8.1-12.2) for TACE alone. At this analysis, a trend toward improvement in overall survival (OS), the trial's other primary endpoint, was observed for the LENVIMA plus KEYTRUDA-based regimen versus TACE alone (HR=0.80 [95% CI, 0.57-1.11]; p=0.0867); the OS data are

not mature and did not reach statistical significance at the time of this interim analysis. The trial is continuing, and follow-up of OS is ongoing. The safety profile of the LENVIMA plus KEYTRUDA-based regimen was consistent with that observed in previously reported studies evaluating the combination.

"Hepatocellular carcinoma is one of the leading causes of cancer-related deaths worldwide, highlighting the need for new treatment options,[1,2]" said Dr. Josep Llovet, Director of the Liver Cancer Program and Professor of Medicine at the Icahn School of Medicine at Mount Sinai. "These findings from the LEAP-012 trial demonstrate the potential of lenvatinib plus pembrolizumab in combination with TACE to extend progression-free survival for patients diagnosed with unresectable, non-metastatic disease."

"Global incidence rates for hepatocellular carcinoma are expected to rise by more than 50 percent over the next two decades and there have been limited advances for patients with unresectable, non-metastatic forms of disease, [3]" said Dr. Gregory Lubiniecki, Vice President, Global Clinical Development, MSD Research Laboratories. "These results reflect our commitment to exploring therapeutic options for these patients, including in earlier stages of disease. We're encouraged by the potential for another treatment option for patients with unresectable non-metastatic hepatocellular carcinoma in addition to the existing monotherapy indications for KEYTRUDA and LENVIMA."

"Transarterial chemoembolization (TACE) has been a standard of care option for patients with unresectable, non-metastatic hepatocellular carcinoma for many years; however, many patients experience disease progression within one year,[4,5,6,7]" said Dr. Corina Dutcus, Senior Vice President, Oncology Global Clinical Development Lead at Eisai Inc. "Data from the Phase 3 LEAP-012 study demonstrate that the addition of LENVIMA plus KEYTRUDA to TACE may help address the unmet need for therapies that can improve progression-free survival for people with this disease. We are grateful to the patients and investigators for their participation in this study."

Treatment was administered to 237 patients receiving the KEYTRUDA plus LENVIMA-based regimen and 241 patients receiving TACE alone. Treatment-related adverse events (TRAEs) occurred in 98.7% of patients receiving LENVIMA plus KEYTRUDA in combination with TACE versus 84.6% of patients receiving TACE alone and led to the discontinuation of both study drugs in 8.4% versus 1.2% of patients, respectively. Serious adverse events were observed in 33.3% of patients receiving LENVIMA plus KEYTRUDA in combination with TACE versus 12.4% of patients receiving TACE alone. Grade 3 or 4 TRAEs occurred in 71.3% of patients receiving LENVIMA plus KEYTRUDA in combination with TACE versus 31.1% for TACE alone and TRAEs led to death in 1.7% (n=4) versus 0.4% (n=1) of patients, respectively.

LENVIMA monotherapy is approved for the treatment of patients with unresectable HCC in more than 80 countries, including in Japan, the U.S., Europe and China.

KEYTRUDA is approved as a monotherapy for the treatment of patients with HCC secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen in the U.S. and as a monotherapy for the treatment of patients with HCC who have been previously treated with sorafenib or oxaliplatin-containing chemotherapy in China.

LENVIMA plus KEYTRUDA is approved in the U.S., the EU, Japan and other countries for the treatment of advanced renal cell carcinoma (RCC) and certain types of advanced endometrial carcinoma. Lenvatinib is marketed as KISPLYX® for advanced RCC in the EU. Eisai and Merck & Co., Inc., Rahway, NJ, USA are studying the LENVIMA plus KEYTRUDA combination through the LEAP (**LE**nvatinib **A**nd **P**embrolizumab) clinical program in various tumor types, including but not limited to HCC, RCC, head and neck cancer, gastric cancer and esophageal cancer across multiple clinical trials.

About LEAP-012

LEAP-012 is a multicenter, randomized, double-blind Phase 3 trial (ClinicalTrials.gov, NCT04246177) evaluating LENVIMA plus KEYTRUDA 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) following a maximum of five 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 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 KEYTRUDA (400 mg intravenously [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 IV placebo administered Q6W plus oral placebo administered once a day in combination with TACE.

All study drugs were continued until protocol-specified discontinuation criteria. KEYTRUDA 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.

About hepatocellular carcinoma

Liver cancer is one of the leading causes of cancer-related deaths worldwide.[1] In the U.S., the incidence rates of liver cancer have more than tripled since 1980, and death rates have doubled during that time. [8] Incidence rates are expected to continue to rise in various regions across the world until 2040, including in countries with advanced healthcare systems.[3] It is estimated there were more than 865,000 new cases of liver cancer and more than 757,000 deaths from the disease globally in 2022.[1] In Japan, it is estimated there were over 41,000 new cases of liver cancer and almost 26,000 deaths from the disease in 2022.[9] In the U.S., it is estimated there will be approximately 42,000 patients diagnosed with liver cancer and almost 30,000 patient deaths from the disease in 2024.[10] The five-year relative survival rate for liver cancer in the U.S. is 22%, based on SEER data from 2013-2019.[11] Hepatocellular carcinoma (HCC) is the most common type of liver cancer, accounting for an estimated 90% of primary liver cancer cases.[12]

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, 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 KEYTRUDA (generic name: 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 KEYTRUDA

(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

About KEYTRUDA® (pembrolizumab) Injection, 100mg

KEYTRUDA is an anti-programmed death receptor-1 (PD-1) therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. KEYTRUDA is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

Merck & Co., Inc., Rahway, NJ, USA has the industry's largest immuno-oncology clinical research program. There are currently more than 1,600 trials studying KEYTRUDA across a wide variety of cancers and treatment settings. The KEYTRUDA clinical program seeks to understand the role of KEYTRUDA across cancers and the factors that may predict a patient's likelihood of benefitting from treatment with KEYTRUDA, including exploring several different biomarkers.

About the Eisai and Merck & Co., Inc., Rahway, NJ, USA Strategic Collaboration

In March 2018, Eisai and Merck & Co., Inc., Rahway, NJ, USA, known as MSD outside of the United States and Canada, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA. Under the agreement, the companies jointly develop, manufacture and commercialize LENVIMA, both as monotherapy and in combination with KEYTRUDA, the anti-PD-1 therapy from Merck & Co., Inc., Rahway, NJ, USA. Eisai and Merck & Co., Inc., Rahway, NJ, USA are studying the LENVIMA plus KEYTRUDA combination through the LEAP (**LE**nvatinib **A**nd **P**embrolizumab) clinical program and are evaluating the combination in various tumor types across multiple clinical trials.

Eisai's Focus on Cancer

Eisai acknowledges "Oncology" as one of its key strategic areas, and will continue to focus on the discovery and development of anti-cancer drugs within drug discovery domains including "microenvironment", "proteostasis disruption", "cell lineage and cell differentiation", and "inflammation, hypoxia, oxidative stress and cell senescence" under the Deep Human Biology Learning (DHBL) drug discovery and development organization. Eisai aspires to discover innovative new drugs with new targets and mechanisms of action from these domains, with the aim of contributing to the cure of cancers.

About Eisai

Eisai's Corporate Concept is "to give first thought to patients and people in the daily living domain, and to increase the benefits that health care provides." Under this Concept [also known as our *human health care* (*hhc*) Concept], we aim to effectively achieve social good in the form of relieving anxiety over health and reducing health disparities. With a global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to create and deliver innovative products to target diseases with high unmet medical needs, with a particular focus in our strategic areas of Neurology and Oncology.

In addition, our continued commitment to the elimination of neglected tropical diseases (NTDs), which is a target (3.3) of the United Nations Sustainable Development Goals (SDGs), is demonstrated by our work on various activities together with global partners.

For more information about Eisai, please visit www.eisai.com (for global headquarters: Eisai. Co., Ltd.), us.eisai.com (for U.S. headquarters: Eisai, Inc.) or www.eisai.eu (for Europe, Middle East, Africa, Russia, Australia and New Zealand headquarters: Eisai Europe Ltd.), and connect with us on X (U.S. and global), LinkedIn (for global, U.S. and EMEA) and Facebook (global).

Merck & Co., Inc., Rahway, NJ, USA's Focus on Cancer

Every day, we follow the science as we work to discover innovations that can help patients, no matter what stage of cancer they have. As a leading oncology company, we are pursuing research where scientific opportunity and medical need converge, underpinned by our diverse pipeline of more than 25 novel mechanisms. With one of the largest clinical development programs across more than 30 tumor types, we strive to advance breakthrough science that will shape the future of oncology. By addressing barriers to clinical trial participation, screening and treatment, we work with urgency to reduce disparities and help ensure patients have access to

high-quality cancer care. Our unwavering commitment is what will bring us closer to our goal of bringing life to more patients with cancer. For more information, visit https://www.merck.com/research/oncology.

About Merck & Co., Inc., Rahway, NJ, USA

At Merck & Co., Inc., Rahway, NJ, USA, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of research to deliver innovative health solutions that advance the prevention and treatment of diseases in people and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe, sustainable and healthy future for all people and communities. For more information, visit www.merck.com and connect with us on X (formerly Twitter), Facebook, Instagram, YouTube and LinkedIn.

Forward-Looking Statement of Merck & Co., Inc., Rahway, NJ, USA

This news release of Merck & Co., Inc., Rahway, NJ, USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline candidates that the candidates will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the

company's patents and other protections for innovation products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's Annual Report on Form 10-K for the year ended December 31, 2023 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

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