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Eisai and Merck & Co., Inc., Rahway, NJ, USA Provide Update on Phase 3 LEAP-012 Trial in Unresectable, Non-Metastatic Hepatocellular Carcinoma

TOKYO and RAHWAY, NJ, Oct. 29, 2025 – 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 that 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) for the treatment of patients with unresectable, non-metastatic hepatocellular carcinoma (HCC).

At a pre-specified interim analysis, LENVIMA plus KEYTRUDA in combination with TACE did not achieve statistical significance for overall survival (OS), one of the study's primary endpoints, compared to TACE alone. The likelihood of reaching the protocol-specified threshold for statistical significance for OS at a future analysis was evaluated by Eisai and Merck & Co., Inc., Rahway, NJ, USA and considered to be low. On this basis, the study will be closed, and the companies are informing investigators of this decision.

The safety profile of the LENVIMA plus KEYTRUDA-based regimen was consistent with that observed in previously reported studies evaluating the combination and in earlier analyses of LEAP-012. Further analysis of the data is ongoing. Eisai and Merck & Co., Inc., Rahway, NJ, USA will work with investigators to share the results with the scientific community.

As reported previously, LENVIMA plus KEYTRUDA in combination with TACE met the study's other primary endpoint of progression-free survival (PFS) and demonstrated a statistically significant and clinically meaningful improvement compared to TACE alone. Data from this first interim analysis, which served as the final analysis for the endpoint of PFS, were presented at the European Society for Medical Oncology (ESMO) Congress 2024 and published in *The Lancet.* With additional follow-up at subsequent analyses, PFS remained consistent.

“Although the progression-free survival results from this study are encouraging, unfortunately, the addition of KEYTRUDA plus LENVIMA to TACE did not show the overall survival benefit we hoped,” said Dr. Gregory Lubiniecki, Vice President, Global Clinical Development, MSD Research Laboratories. “We are grateful to the patients and investigators for their important contributions to this study, and our commitment is unwavering as we pursue new therapeutic options for people living with hepatocellular carcinoma, an aggressive and challenging-to-treat cancer.”

“The overall survival findings from LEAP-012, along with the previously reported improvement in progression-free survival, provide important insights for treating unresectable, non-metastatic hepatocellular carcinoma,” said Dr. Corina Dutcus, Senior Vice President, Oncology Global Clinical Development Lead at Eisai. “For years, TACE has been a standard of care for these patients, yet many experience disease progression within twelve months. With LEAP-012, we sought to make a meaningful difference for this patient population. LENVIMA continues to play an important role as a monotherapy treatment option for patients with unresectable HCC, and as a company with a deep heritage in liver cancer research, Eisai remains committed to advancing the science.”

In July 2025, LENVIMA plus KEYTRUDA in combination with TACE was approved in China to treat unresectable non-metastatic HCC. The LENVIMA plus KEYTRUDA combination is approved in the U.S., the European Union (EU), Japan and other countries for the treatment of advanced renal cell carcinoma (RCC) and certain types of advanced endometrial carcinoma. Results from the LEAP-012 trial do not affect the current approved indications for the LENVIMA plus KEYTRUDA combination, including the approval of LENVIMA plus KEYTRUDA in combination with TACE in China to treat unresectable non-metastatic HCC.

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

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.

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) 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), 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.[2] 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 866,000 new cases of liver cancer and more than 758,000 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.[4] 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 2025.[5] The five-year relative survival rate for liver cancer in the U.S. is 22%, based on Surveillance, Epidemiology, and End Results (SEER) data from 2015-2021.[6] Hepatocellular carcinoma is the most common type of liver cancer, accounting for an estimated 85%-90% of primary liver cancer cases.[7]

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

- Indication in combination with KEYTRUDA (generic name: pembrolizumab) and transarterial chemoembolization (Approved in China)

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 KEYTRUDA

(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 that is pMMR or not microsatellite instability-high (MSI-H), as determined by an FDA-approved test, 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 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 for intravenous use, 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 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'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", and "cell lineage and cell differentiation" 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 innovative 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, 2024 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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[7] Llovet JM et al. Hepatocellular carcinoma. *Nature Reviews.* 2021 7:6. https://www.nature.com/articles/s41572-020-00240-3.pdf.

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