

Eisai Co., Ltd.
Public Relations:
+81-(0) 3-3817-5120

Eisai Co., Ltd.
Investor Relations:
+81-(0)70-8688-9685

Merck & Co., Inc., Rahway, NJ, USA
Media Relations
Melissa Moody: +1-(215) 407-3536
Nikki Sullivan: +1-(718) 644-0730

Merck & Co., Inc., Rahway, NJ, USA
Investor Relations
Peter Dannenbaum: +1-(908) 740-1037
Damini Chokshi: +1-(908) 740-1807

Eisai and Merck & Co., Inc., Rahway, NJ, USA Provide Update on Phase 3 LEAP-002 Trial Evaluating LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Versus LENVIMA Monotherapy in Patients With Unresectable Hepatocellular Carcinoma

TOKYO and RAHWAY, N.J., August 3, 2022 – Eisai (Headquarters: Tokyo, CEO: Haruo Naito, “Eisai”) and Merck & Co., Inc., Rahway, NJ, USA (known as MSD outside the United States and Canada) today announced that the Phase 3 LEAP-002 trial investigating LENVIMA®, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, plus KEYTRUDA®, the anti-PD-1 therapy from Merck & Co., Inc., Rahway, NJ, USA, versus LENVIMA monotherapy did not meet its dual primary endpoints of overall survival (OS) and progression-free survival (PFS) as a first-line treatment for patients with unresectable hepatocellular carcinoma (uHCC). There were trends toward improvement in OS and PFS for patients who received LENVIMA plus KEYTRUDA versus LENVIMA monotherapy; however, these results did not meet statistical significance per the pre-specified statistical plan. The median OS of the LENVIMA monotherapy arm in LEAP-002 was longer than that observed in previously reported clinical trials evaluating LENVIMA monotherapy in uHCC. The safety profile of LENVIMA plus KEYTRUDA was consistent with previously reported data on the combination. Eisai and Merck & Co., Inc., Rahway, NJ, USA plan to present these data at an upcoming medical conference.

“Our joint clinical development program for KEYTRUDA plus LENVIMA is designed to address unmet needs for some of the most challenging-to-treat types of cancer, like hepatocellular carcinoma,” said Dr. Gregory Lubiniecki, Vice President, Global Clinical Development, Merck & Co., Inc., Rahway, NJ, USA Research Laboratories. “We remain confident in the potential of this combination based on the body of evidence we’ve seen to date and will continue to investigate its role across multiple types of cancer.”

“Aiming for further improvement in the treatment of patients with unresectable HCC, we selected LENVIMA monotherapy, a standard of care option, as the control arm of the LEAP-002

trial,” said Corina Dutcus, M.D., Senior Vice President, Clinical Research, Oncology at Eisai Inc. “While results evaluating the combination are not what we had hoped for, we will continue to contribute to the care of patients with unresectable HCC by applying valuable knowledge from the LEAP-002 trial.”

LENVIMA monotherapy is approved for the first-line treatment of patients with uHCC in the U.S., Europe, and China, and for patients with uHCC in Japan. The approval of LENVIMA was based on results of the Phase 3 REFLECT trial which evaluated the efficacy and safety of LENVIMA versus sorafenib for the first-line treatment of patients with uHCC.

In the U.S., LENVIMA plus KEYTRUDA is approved for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high or mismatch repair deficient, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation and for adult patients with advanced renal cell carcinoma (RCC) in the first-line setting. In Europe, LENVIMA (marketed as KISPLYX® for RCC in the EU) plus KEYTRUDA is approved for 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 or radiation and for adults with advanced RCC in the first-line setting. The LENVIMA plus KEYTRUDA combination is also approved in Japan for patients with radically unresectable or metastatic RCC and patients with unresectable, advanced or recurrent endometrial carcinoma that progressed after cancer chemotherapy. Results from the LEAP-002 trial do not affect the current approved indications for the LENVIMA and KEYTRUDA combination.

Eisai and Merck & Co., Inc., Rahway, NJ, USA are studying the LENVIMA plus KEYTRUDA combination through the LEAP (LEnvatinib And Pembrolizumab) clinical program in more than 10 different tumor types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, head and neck cancer, biliary tract cancer, colorectal cancer, gastric cancer, esophageal cancer, glioblastoma and pancreatic cancer) across more than 15 clinical trials.

About LEAP-002

LEAP-002 is a multicenter, randomized, double-blinded, active-controlled Phase 3 trial (ClinicalTrials.gov, [NCT03713593](https://clinicaltrials.gov/ct2/show/study/NCT03713593)) evaluating LENVIMA plus KEYTRUDA versus LENVIMA monotherapy for the first-line treatment of adult patients with uHCC. The dual primary endpoints are PFS, as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors Version (RECIST) v1.1 (RECIST v1.1 has been modified for this study to

follow a maximum of 10 target lesions in total and a maximum of 5 target lesions per organ), and OS. The secondary endpoints include ORR, as assessed by BICR per RECIST v1.1, and DOR. The study enrolled 794 patients who were randomized 1:1 to receive:

- LENVIMA (12 mg orally once daily [for patients with screening body weight of at least 60 kg] or 8 mg orally once daily [for patients with screening body weight less than 60 kg]) plus KEYTRUDA (200 mg intravenously [IV] on Day 1 of each three-week cycle); or
- LENVIMA (12 mg orally once daily [for patients with screening body weight of at least 60 kg] or 8 mg orally once daily [for patients with screening body weight less than 60 kg]) plus saline placebo (IV administered on Day 1 of each three-week cycle).

LENVIMA was administered until progressive disease or unacceptable toxicity. KEYTRUDA /placebo was administered for up to 35 cycles (approximately two years).

About Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma is the most common type of primary liver cancer¹ and the most rapidly increasing cause of cancer deaths in the United States.² Hepatocellular carcinoma accounts for approximately 90% of primary liver cancers.³ It is estimated there were more than 905,000 new cases of liver cancer and more than 830,000 deaths from the disease globally in 2020,⁴ making it the sixth most frequently diagnosed cancer worldwide⁵ and one of the leading causes of cancer deaths around the world.⁵ In Japan, it is estimated there were more than 45,000 new cases of liver cancer diagnosed and more than 28,000 deaths from this disease in 2020.⁶ In the United States, it is estimated there will be over 41,000 new cases of liver cancer and over 30,000 deaths from this disease in 2022.⁵ Risk factors for liver cancer include gender, ethnicity, chronic viral hepatitis (Hep-B or Hep-C) infection, cirrhosis, alcohol use and metabolic syndrome.⁷ Hepatocellular carcinoma, which is often diagnosed at an advanced stage,⁸ has a five-year survival rate of approximately 20% in the U.S.⁹

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 (PDGFR α), 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 in over 80 countries including Japan, the United States, China, and countries in Europe and Asia)

Japan: Radically 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 in over 80 countries including Japan, the United States, China, and countries in Europe 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 in over 65 countries including the United States, and countries in 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 in over 40 countries including Japan, the United States, and countries in 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 [including conditional approval] in over 45 countries including Japan, the United States, and countries in 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-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 1,700 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 Eisai and the Merck & Co., Inc., Rahway, NJ, USA 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 will 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.

In addition to ongoing clinical studies evaluating the LENVIMA plus KEYTRUDA combination across several different tumor types, the companies have jointly initiated new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program and are evaluating the combination in more than 10 different tumor types across more than 20 clinical trials.

Eisai's Focus on Cancer

Eisai focuses on the development of anticancer drugs, targeting the tumor microenvironment (with experience and knowledge from existing in-house discovered compounds) and the driver gene mutation and aberrant splicing (leveraging RNA Splicing Platform) as areas (*Ricchi*) where real patient needs are still unmet, and where Eisai can aim to become a frontrunner in oncology. Eisai aspires to discover innovative new drugs with new targets and mechanisms of action from these *Ricchi*, 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 Twitter ([U.S.](#) and [global](#)) and LinkedIn (for [U.S.](#) and [EMEA](#)).

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

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck & Co., Inc., Rahway, NJ, USA, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck & Co., Inc., Rahway, NJ, USA is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

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

For over 130 years, Merck & Co., Inc., Rahway, NJ, USA, known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck & Co., Inc., Rahway, NJ, USA continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit www.merck.com and connect with us on [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 the global outbreak of novel coronavirus disease (COVID-19); 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, 2021 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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- ³ Eunsun K., et al. Hepatocellular carcinoma: old friends and new tricks. *Experimental & Molecular Medicine Cancer*. 2020. Dec;52(12):1898-1907. <https://www.nature.com/articles/s12276-020-00527-1.pdf> .
- ⁴ International Agency for Research on Cancer, World Health Organization. "Liver Fact Sheet." Cancer Today, 2020. <https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf> .
- ⁵ American Cancer Society website, "Key Statistics About Liver Cancer." accessed 7/27/2022: <https://www.cancer.org/cancer/liver-cancer/about/what-is-key-statistics.html> .
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- ⁸ Stefano C., et al. Challenges of advanced hepatocellular carcinoma. *World J Gastroenterol*. 2016 Sep 14; 22(34): 7645–7659. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5016365/pdf/WJG-22-7645.pdf> .
- ⁹ National Cancer Institute. "SEER Cancer Statistics Review 1975-2016." https://seer.cancer.gov/archive/csr/1975_2016/results_merged/topic_survival.pdf .

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