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Eisai and Merck & Co., Inc., Rahway, NJ, USA Provide Update on Phase 3 Trials of LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) in Certain Patients With Advanced Melanoma (LEAP-003) and Metastatic Colorectal Cancer (LEAP-017)

TOKYO and RAHWAY, N.J., Apr. 7, 2023 – Eisai (Headquarters: Tokyo, CEO: Haruo Naito) and Merck & Co., Inc., Rahway, NJ, USA (known as MSD outside of the United States and Canada) today provided updates on two Phase 3 trials, LEAP-003 and LEAP-017 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.

LEAP-003: Eisai and Merck & Co., Inc., Rahway, NJ, USA are discontinuing the Phase 3 LEAP-003 trial evaluating LENVIMA plus KEYTRUDA for the first-line treatment of adults with unresectable or metastatic melanoma. This decision is based on the recommendation of an independent Data Monitoring Committee (DMC), which reviewed data from a planned interim analysis and determined LENVIMA plus KEYTRUDA did not demonstrate an improvement in overall survival (OS), one of the study's dual primary endpoints, versus KEYTRUDA alone. Eisai and Merck & Co., Inc., Rahway, NJ, USA are informing study investigators of the decision and advising them to reach out to patients in the study regarding treatment. At an earlier interim analysis, the trial's other dual primary endpoint, progression-free survival (PFS), showed a statistically significant improvement in the LENVIMA plus KEYTRUDA arm versus the KEYTRUDA plus placebo arm.

LEAP-017: The Phase 3 LEAP-017 trial evaluating LENVIMA plus KEYTRUDA did not meet its primary endpoint of OS for the treatment of patients with unresectable and metastatic colorectal cancer that is mismatch repair proficient (pMMR) or not microsatellite instability-high (MSI-H) who experienced disease progression on, or became intolerant to, prior therapy. In the final pre-specified analysis of OS, a trend toward improvement was observed with LENVIMA plus KEYTRUDA versus regorafenib or TAS-102 (trifluridine and tipiracil hydrochloride); however, these results did not meet statistical significance per the pre-specified statistical analysis plan. A

trend toward improvement was also observed in key secondary endpoints of PFS, objective response rate (ORR) and duration of response (DOR) with LENVIMA plus KEYTRUDA versus regorafenib or TAS-102; however, per the pre-specified statistical analysis plan, these results were not tested for statistical significance.

In both the LEAP-003 and LEAP-017 trials, the safety profile of LENVIMA plus KEYTRUDA was consistent with previously reported data on the combination. A full evaluation of the data from these studies including pre-planned key subgroup analyses is ongoing. The companies will work with investigators to share the results with the scientific community.

“We are grateful to all the investigators, patients and their families for their participation in these studies, and we will continue to evaluate KEYTRUDA plus LENVIMA across different types of cancer where additional treatment options are needed. We remain fully committed to building on existing treatments, as part of our efforts to help as many appropriate patients with cancer as we can,” said Dr. Gregory Lubiniecki, Vice President, Global Clinical Development, Merck & Co., Inc., Rahway, NJ, USA Research Laboratories.

“With the LEAP-003 and LEAP-017 trials, we set out to help improve outcomes for patients with two difficult-to-treat advanced cancers, melanoma and colorectal cancer,” said Corina Dutcus, M.D., Senior Vice President, Clinical Development, Oncology at Eisai Inc. “While these results are different from our initial expectation, insights from both studies will help contribute to our understanding of LENVIMA plus KEYTRUDA. We remain confident in LENVIMA as a pillar of Eisai’s oncology portfolio and will continue to evaluate its potential in ongoing trials within the LEAP program.”

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. Results from the LEAP-003 and LEAP-017 trials 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 multiple tumor types, including but not limited to endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, RCC, head and neck cancer, colorectal cancer, gastric cancer and esophageal cancer, across more than 10 clinical trials.

About LEAP-003

LEAP-003 is a randomized, placebo-controlled Phase 3 trial ([ClinicalTrials.gov, NCT03820986](https://clinicaltrials.gov/ct2/show/study/NCT03820986)) evaluating LENVIMA plus KEYTRUDA versus KEYTRUDA alone for the first-line treatment of adults with unresectable or metastatic melanoma. The dual primary endpoints are OS and PFS, as assessed by Response Evaluation Criteria in Solid Tumors version 1.1

(RECIST v1.1). Key secondary endpoints include ORR and DOR, both as assessed by RECIST v1.1, and safety. The study enrolled 674 patients who were randomized 1:1 to receive:

- LENVIMA (20 mg orally once daily) plus KEYTRUDA (200 mg intravenously [IV] on Day 1 of each three-week cycle); or
- placebo via oral capsule daily plus KEYTRUDA (200 mg IV on Day 1 of each three-week cycle)

KEYTRUDA was administered for up to 35 cycles (approximately two years) or until protocol-specified discontinuation criteria were met. After completing two years of combination therapy, LENVIMA may have been administered as a single agent until protocol-specified discontinuation criteria were met.

About Melanoma

Melanoma, the most serious form of skin cancer, is characterized by the uncontrolled growth of melanocytes, pigment producing cells.¹ The rates of melanoma have been rising over the past few decades, with nearly 325,000 new cases diagnosed worldwide in 2020.^{1,2} In the U.S., skin cancer is one of the most common types of cancer diagnosed. Although melanoma accounts for only 1% of skin cancers, it accounts for a large majority of skin cancer deaths.¹ It is estimated there will be nearly 100,000 new cases of melanoma diagnosed and approximately 8,000 deaths resulting from the disease in the U.S. in 2023.¹ The five-year survival rates from 2012-2018 are estimated to be 71% for regional disease and 32% for distant disease.³

About LEAP-017

LEAP-017 is a randomized, open label, Phase 3 trial (ClinicalTrials.gov, [NCT04776148](https://clinicaltrials.gov/ct2/show/study/NCT04776148)) evaluating LENVIMA plus KEYTRUDA versus regorafenib or TAS-102, for patients with unresectable and metastatic colorectal cancer that is pMMR or not MSI-H who have received and progressed on or after, or became intolerant to, prior treatment. Patients must have been previously treated for colorectal cancer and have shown disease progression as defined by RECIST v1.1 on or after, or could not tolerate, standard treatment. The standard treatment must include all of the following agents, if approved and locally available in the country where the participant is randomized:

- Fluoropyrimidine, irinotecan and oxaliplatin;
 - With or without an anti-vascular endothelial growth factor monoclonal antibody (bevacizumab);
 - With anti-epidermal growth factor receptor monoclonal antibodies (cetuximab or panitumumab) for RAS (KRAS/NRAS) wild-type (WT) participants; and

- BRAF inhibitor (in combination with cetuximab +/- binimetinib) for BRAF V600E mutated metastatic colon cancer.

The primary endpoint is OS and key secondary endpoints include PFS, ORR and DOR, according to RECIST v1.1 per blinded independent central review (BICR). The study enrolled 480 patients randomized 1:1 to receive:

- LENVIMA (20 mg given orally once daily) plus KEYTRUDA (400 mg IV on Day 1 of each six-week cycle); or
- Regorafenib (160 mg given orally once daily on Days 1 through 21 of each four-week cycle; or TAS-102 (35mg/m² given orally twice daily on Days 1 through 5 and Days 8 through 12 of each four-week cycle).

KEYTRUDA was administered for up to 18 cycles (approximately two years), or until protocol-specified discontinuation criteria were met. After completing two years of combination therapy, LENVIMA may have been administered as a single agent until protocol-specified discontinuation criteria were met.

About colorectal cancer

Colorectal cancer can be referred to as colon cancer or rectal cancer, depending on where the cancer starts.⁴ Colorectal cancer often begins with growths on the inner lining of the colon or rectum called polyps, which can change into cancer over time.⁴ Colorectal cancer is the third most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide.⁵ It is estimated there were more than 1,880,000 new cases of colorectal cancer globally in 2020.⁵ In Japan, it is estimated there were more than 147,000 new cases of colorectal cancer diagnosed and more than 59,000 deaths from this disease in 2020.⁶ In the United States, it is estimated there will be approximately 107,000 new cases of colon cancer and approximately 46,000 new cases of rectal cancer, resulting in more than 52,000 deaths from colorectal cancer in 2023.⁷ The five-year relative survival rates in the U.S. for metastatic colon cancer and rectal cancer (stage IV) are estimated to be 13% and 17%, respectively.⁸

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: 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 mismatch repair proficient (pMMR), as determined by an FDA-approved test, or not microsatellite instability-high (MSI-H), 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 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 clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program and are evaluating the combination in multiple tumor types across more than 10 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 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, 2022 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

¹ American Cancer Society. Key Statistics for Melanoma Skin Cancer. <https://www.cancer.org/cancer/melanoma-skin-cancer/about/key-statistics.html> .

² International Agency for Research on Cancer, World Health Organization. "Skin Fact Sheet." Cancer Today, 2020. <https://gco.iarc.fr/today/data/factsheets/cancers/16-Melanoma-of-skin-fact-sheet.pdf> .

³ National Cancer Institute, Surveillance, Epidemiology, and End Results Program. "Cancer Stat Facts: Melanoma of the Skin" <https://seer.cancer.gov/statfacts/html/melan.html> .

⁴ American Cancer Society. "What is Colorectal Cancer?" About Colorectal cancer. <https://www.cancer.org/cancer/colon-rectal-cancer/about/what-is-colorectal-cancer.html> .

⁵ Cancer. Net[®]. Colorectal Cancer: Statistics <https://www.cancer.net/cancer-types/colorectal-cancer/statistics> .

⁶ International Agency for Research on Cancer, World Health Organization. "Japan Fact Sheet." Cancer Today, 2020. <https://gco.iarc.fr/today/data/factsheets/populations/392-japan-fact-sheets.pdf> .

⁷ American Cancer Society. Cancer Facts & Figures 2023. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf> .

⁸ American Cancer Society. "Survival Rates for Colorectal Cancer" Early detection, Diagnosis, and Staging. <https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html> .

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