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LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Demonstrates Long-Term, Durable Survival Benefit Versus Sunitinib as First-Line Treatment for Patients With Advanced Renal Cell Carcinoma

After four years of follow-up, LENVIMA plus KEYTRUDA reduced the risk of death by 21% versus sunitinib in the pivotal Phase 3 CLEAR (Study 307)/KEYNOTE-581 trial

Final results will be presented at ASCO 2023 in an oral abstract session

TOKYO and RAHWAY, N.J., May.26, 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 announced data from the final pre-specified overall survival (OS) analysis of the pivotal Phase 3 CLEAR (Study 307)/KEYNOTE-581 trial investigating LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, plus KEYTRUDA, Merck's anti-PD-1 therapy, for the first-line treatment of patients with advanced renal cell carcinoma (RCC). These data will be presented on Monday, June 5 at 11:54 a.m. Central Daylight Time during an oral abstract session at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract #4502).

After four years of follow-up, LENVIMA plus KEYTRUDA maintained a clinically meaningful OS benefit versus sunitinib, reducing the risk of death by 21% (HR=0.79 [95% CI, 0.63-0.99]). The 24- and 36-month estimated OS rates were 80.4% and 66.4% for LENVIMA plus KEYTRUDA versus 69.6% and 60.2% for sunitinib, respectively. Results from the final pre-specified OS analysis were consistent with the superior results versus sunitinib from the primary OS analysis of the CLEAR/KEYNOTE-581 trial.

Additionally, LENVIMA plus KEYTRUDA reduced the risk of disease progression or death by 53% (HR=0.47 [95% CI, 0.38-0.57]), with a median progression-free survival (PFS) of 23.9 months (95% CI, 20.8-27.7) for LENVIMA plus KEYTRUDA versus 9.2 months (95% CI, 6.0-11.0)

for sunitinib; the objective response rate (ORR) was 71.3% (95% CI, 66.6-76.0) with a complete response (CR) rate of 18.3% for LENVIMA plus KEYTRUDA versus an ORR of 36.7% (95% CI, 31.7-41.7) with a CR rate of 4.8% for sunitinib.

There were no new safety signals and the safety profile at the final OS analysis was consistent with the primary analysis. Grade ≥ 3 treatment-related adverse events (TRAE) occurred in 74.1% of patients who received LENVIMA plus KEYTRUDA versus 60.3% of patients who received sunitinib. The six most common TRAEs of any grade of patients in the LENVIMA plus KEYTRUDA arm were diarrhea (56.0%), hypertension (54.3%), hypothyroidism (44.9%), decreased appetite (35.5%), fatigue (34.1%) and stomatitis (32.7%). In the sunitinib arm, the six most common TRAEs of any grade were diarrhea (45.3%), hypertension (40.3%), stomatitis (37.4%), palmar-plantar erythrodysesthesia (36.2%), fatigue (32.9%) and nausea (28.2%).

“LENVIMA plus KEYTRUDA continues to demonstrate durable clinical benefit as a first-line treatment for patients with advanced renal cell carcinoma, as shown by the clinically meaningful improvement in overall survival sustained with four years of follow up,” said Dr. Thomas Hutson, DO, Pharm.D., FACP, Director of the Urologic Oncology Program and Co-chair of the Urologic Cancer Research and Treatment Center, Texas Oncology at Baylor Sammons Cancer Center. “Furthermore, these data also showed clinically meaningful improvements in median PFS and ORR compared to sunitinib. These findings reinforce the important role of LENVIMA plus KEYTRUDA as a first-line standard of care treatment option for patients with advanced renal cell carcinoma.”

“Long-term follow up data from the CLEAR/KEYNOTE-581 trial show the responses to first-line use of KEYTRUDA plus LENVIMA were durable for many of these patients,” said Dr. Gregory Lubiniecki, Vice President, Global Clinical Development, Merck Research Laboratories. “Through our joint clinical development program with Eisai, we’re continuing to advance our research evaluating KEYTRUDA plus LENVIMA for other challenging cancers as we strive to help even more patients.”

“At the final pre-specified analysis, LENVIMA plus KEYTRUDA continued to demonstrate clinically meaningful efficacy across PFS, ORR and OS, providing patients and their physicians with new information about treating people living with advanced renal cell carcinoma,” said Corina Dutcus, M.D., Senior Vice President, Clinical Development, Oncology at Eisai Inc. “These results are a testament to our steadfast commitment to people living with advanced cancers, and we are grateful for the support from the patients, families and healthcare provider community for their participation in this research.”

LENVIMA plus KEYTRUDA is approved in the U.S., the EU, Japan and other countries for the treatment of advanced RCC and certain types of advanced endometrial carcinoma. Lenvatinib is marketed as KISPLYX® for advanced RCC in the EU. Eisai and Merck are studying the LENVIMA plus KEYTRUDA combination through the LEAP (LEnvatinib And Pembrolizumab) clinical program in various tumor types, including but not limited to endometrial carcinoma,

hepatocellular carcinoma, non-small cell lung cancer, RCC, head and neck cancer, gastric cancer and esophageal cancer across multiple clinical trials.

Study design and additional data from CLEAR/KEYNOTE-581

The CLEAR/KEYNOTE-581 trial is a multicenter, randomized, open-label Phase 3 trial (ClinicalTrials.gov, NCT02811861) evaluating LENVIMA in combination with KEYTRUDA or in combination with everolimus versus sunitinib for the first-line treatment of patients with advanced RCC. The major efficacy outcome measures were PFS, as assessed by independent radiologic review (IRC) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and OS. Additional efficacy outcome measures included confirmed ORR as assessed by IRC, health-related quality of life (HRQoL) and safety.

The trial enrolled 1,069 patients who were randomized 1:1:1 to receive LENVIMA (20 mg orally once daily) plus KEYTRUDA (200 mg intravenously every three weeks for up to 24 months), or LENVIMA (18 mg orally once daily) plus everolimus (5 mg orally once daily), or sunitinib (50 mg orally once daily for four weeks on treatment, followed by two weeks off treatment). 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.

This final pre-specified OS analysis was event driven and was triggered by approximately 304 OS target events in the two treatment arms (149 events out of 355 patients for KEYTRUDA plus LENVIMA versus 159 events out of 357 patients for sunitinib).

The median duration of response was 26.7 months (95% CI, 22.8-34.6) for LENVIMA plus KEYTRUDA versus 14.7 months (95% CI, 9.4-18.2) for sunitinib.

Efficacy results were consistent across the pre-specified Memorial Sloan Kettering Cancer Center (MSKCC) risk groups (favorable, intermediate and poor) and International Metastatic RCC Database Consortium (IMDC) risk groups. Across the pre-specified Memorial Sloan Kettering Cancer Center (MSKCC) risk groups (favorable, intermediate and poor), OS and PFS were improved with LENVIMA plus KEYTRUDA versus sunitinib. Interpretation OS in favorable risk patients is limited by low number of events.

Fewer patients who were treated with LENVIMA plus KEYTRUDA received subsequent anti-cancer therapies (181 out of 355 patients, 51.0%) versus those who were treated with sunitinib (246 out of 357 patients, 68.9%), with 56 patients (15.8%) and 195 patients (54.6%) who went on to receive PD-1/PD-L1 checkpoint inhibitors, respectively. In an exploratory analysis using a 2-stage model, LENVIMA plus KEYTRUDA reduced the risk of death by 45% versus sunitinib when adjusted for subsequent anticancer medications (HR=0.55 [95% CI, 0.44-0.69]).

About renal cell carcinoma (RCC)

Worldwide, it is estimated there were more than 431,000 new cases of kidney cancer diagnosed and more than 179,000 deaths from the disease in 2020. ¹ Renal cell carcinoma is by far the most common type of kidney cancer; about nine out of 10 kidney cancer diagnoses are RCC. ² Renal cell carcinoma is about twice as common in men as in women. ³ Most cases of RCC are discovered incidentally during imaging tests for other abdominal diseases. ⁴ Approximately 30% of patients with RCC will have metastatic disease at diagnosis. ⁴ Survival is highly dependent on the stage at diagnosis, and the five-year survival rate is 15% for patients diagnosed with metastatic disease. ⁵

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

(Approved in over 45 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 International Agency for Research on Cancer, World Health Organization. “Kidney Fact Sheet.” Cancer Today, 2020. <https://gco.iarc.fr/today/data/factsheets/cancers/29-Kidney-fact-sheet.pdf> .

² American Cancer Society. “What Is Kidney Cancer?” About Kidney Cancer. <https://www.cancer.org/cancer/types/kidney-cancer/about/what-is-kidney-cancer.html> .

³ American Cancer Society. "Key Statistics About Kidney Cancer" About Kidney Cancer.

<https://www.cancer.org/cancer/types/kidney-cancer/about/key-statistics.html> .

⁴ American Family Physician. Renal Cell Carcinoma: Diagnosis and Management.

<https://www.aafp.org/pubs/afp/issues/2019/0201/p179.html> .

⁵ American Cancer Society. "Survival Rates for Kidney Cancer" Early detection, Diagnosis, and Staging.

<https://www.cancer.org/cancer/types/kidney-cancer/detection-diagnosis-staging/survival-rates.html> .

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