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LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Approved in Japan for Radically Unresectable or Metastatic Renal Cell Carcinoma

Results From CLEAR/KEYNOTE-581 Showed LENVIMA Plus KEYTRUDA Significantly Reduced the Risk of Disease Progression or Death by 61%, With a Median Progression-Free Survival of Nearly Two Years Versus Nine Months for Sunitinib

LENVIMA Plus KEYTRUDA Now Approved in Japan for Two Types of Cancer

TOKYO and KENILWORTH, N.J., February 25, 2022 – Eisai (Headquarters: Tokyo, CEO: Haruo Naito) and Merck & Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the United States and Canada) today announced that the Japanese Ministry of Health, Labour and Welfare (MHLW) has approved the combination of LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, plus KEYTRUDA, the anti-PD-1 therapy from Merck & Co., Inc., Kenilworth, N.J., U.S.A., for radically unresectable or metastatic renal cell carcinoma (RCC). LENVIMA plus KEYTRUDA is also approved in the U.S. and Europe for the first-line treatment of adult patients with advanced RCC. This marks the second approval of this combination in Japan; in December 2021, LENVIMA plus KEYTRUDA was approved for unresectable, advanced or recurrent endometrial carcinoma that progressed after chemotherapy.

The approval is based on results from the pivotal Phase 3 CLEAR (Study 307)/KEYNOTE-581 trial, in which LENVIMA plus KEYTRUDA demonstrated statistically significant improvements versus sunitinib in the primary efficacy outcome measure of progression-free survival (PFS). Results showed LENVIMA plus KEYTRUDA (n=355) reduced the risk of disease progression or death by 61% (HR=0.39 [95% CI, 0.32-0.49]; p<0.0001), with a median PFS of 23.9 months versus 9.2 months for sunitinib (n=357).

“Nearly one in three cases of renal cell carcinoma are diagnosed at an advanced stage,¹ and patients are in need of new treatment options that may improve survival outcomes,²” said Dr. Gregory Lubiniecki, Vice President, Oncology Clinical Research, Merck & Co., Inc., Kenilworth,

N.J., U.S.A. Research Laboratories. “In the CLEAR/KEYNOTE-581 trial, KEYTRUDA plus LENVIMA reduced the risk of disease progression or death by 61% versus sunitinib, a current standard of care. We are encouraged that patients with certain types of advanced renal cell carcinoma may have the opportunity to benefit from this combination.”

“Today’s milestone for LENVIMA plus KEYTRUDA as a treatment for radically unresectable or metastatic renal cell carcinoma is particularly exciting as it marks the second approval for the combination in Japan,” said Terushige Iike, President of Eisai Japan, Senior Vice President, Eisai. “We are thrilled to be able to provide Japanese patients with a new treatment option, illustrating our shared commitment with Merck & Co., Inc., Kenilworth, N.J., U.S.A. to develop therapies with the aim of addressing the unmet needs of those living with difficult-to-treat cancers. We would like to thank the patients, families and healthcare providers who made this approval possible.”

The Japanese package inserts for LENVIMA and KEYTRUDA note that in the CLEAR/KEYNOTE-581 trial, adverse reactions were observed in 341 (96.9%) of 352 patients (including 42 of 42 Japanese patients) in the safety analysis set. The most common adverse reactions included diarrhea in 192 patients (54.5%), hypertension in 184 patients (52.3%), hypothyroidism in 150 patients (42.6%), decreased appetite in 123 patients (34.9%), fatigue in 113 patients (32.1%), stomatitis in 113 patients (32.1%), palmar-plantar erythrodysesthesia syndrome in 99 patients (28.1%), proteinuria in 97 patients (27.6%), nausea in 94 patients (26.7%), dysphonia in 87 patients (24.7%), rash in 77 patients (21.9%), and asthenia in 71 patients (20.2%).

Renal cell carcinoma is the most common type of kidney cancer worldwide; about nine out of 10 kidney cancer diagnoses are RCC.³ In Japan, there were more than 25,000 new cases of kidney cancer diagnosed and more than 8,000 deaths from the disease in 2020.⁴ Approximately 30% of patients with RCC will have metastatic disease at diagnosis.⁵ Survival is highly dependent on the stage at diagnosis, and with a five-year survival rate of 14% for patients diagnosed with metastatic disease, the prognosis for these patients is poor.⁶

Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A. continue to study the LENVIMA plus KEYTRUDA combination across several types of cancer with more than 20 clinical trials.

About CLEAR/KEYNOTE-581 Trial⁷

The approval is based on data from CLEAR (Study 307)/KEYNOTE-581 (ClinicalTrials.gov, [NCT02811861](https://clinicaltrials.gov/ct2/show/study/NCT02811861)), a Phase 3, multicenter, open-label, randomized trial conducted in 1,069 patients with advanced RCC in the first-line setting. The primary efficacy outcome was PFS as assessed by blinded independent central review (BICR) according to RECIST v1.1. Key secondary efficacy outcome measures were overall survival and objective response rate.

Patients 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). Treatment continued until unacceptable toxicity or disease progression as determined by investigator and confirmed by BICR using RECIST v1.1. If disease progression was observed by imaging evaluation, clinically stable patients with no symptoms indicating disease progression were allowed to continue on study treatment until disease progression was observed in a subsequent imaging evaluation.

About LENVIMA® (lenvatinib) Capsules

LENVIMA, discovered and developed by Eisai, is an orally available 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.

Currently, LENVIMA has been approved for monotherapy as a treatment for thyroid cancer in over 75 countries including Japan, in Europe, China and elsewhere in Asia, and in the United States for locally recurrent or metastatic, progressive, radioiodine-refractory differentiated thyroid cancer. In addition, LENVIMA has been approved for monotherapy as a treatment for unresectable hepatocellular carcinoma in over 70 countries including Japan, in Europe, China and in Asia, and in the United States for first-line unresectable hepatocellular carcinoma. LENVIMA has been approved for monotherapy as a treatment for unresectable thymic carcinoma in Japan. It is also approved in combination with everolimus as a treatment for renal cell carcinoma following prior antiangiogenic therapy in over 60 countries, including in Europe and Asia, and in the United States the treatment of adult patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma. LENVIMA has been approved in combination with KEYTRUDA (generic name: pembrolizumab), for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) in United States and in Europe. LENVIMA has been approved in combination with KEYTRUDA as a treatment for advanced endometrial carcinoma 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 in the United States, and has been approved for the similar indication (including conditional approval) in over 10 countries such as Canada and Australia. In some regions, continued approval for this indication is contingent upon verification and description of clinical benefit in the confirmatory trials. In Europe, it has been approved in combination with KEYTRUDA

(generic name: pembrolizumab) as the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation. In Japan, it has been approved in combination with KEYTRUDA (generic name: pembrolizumab) for the treatment of patients with unresectable advanced or recurrent endometrial carcinoma that progressed after cancer chemotherapy and with radically unresectable or metastatic renal cell carcinoma.

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., Kenilworth, N.J., U.S.A. 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 the Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A. Strategic Collaboration

In March 2018, Eisai and Merck & Co., Inc., Kenilworth, N.J., U.S.A., 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., Kenilworth, N.J., U.S.A.

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 is a leading global research and development-based pharmaceutical company headquartered in Japan, with approximately 10,000 employees worldwide. We define our corporate mission as “giving first thought to patients and their families and to increasing the benefits health care provides,” which we call our *human health care (hhc)* philosophy. We strive to realize our *hhc* philosophy by delivering innovative products in therapeutic areas with high unmet medical needs, including Oncology and Neurology. In the spirit of *hhc*, we take that commitment even further by applying our scientific expertise, clinical capabilities and patient insights to discover and develop innovative solutions that help address society’s toughest unmet needs, including neglected tropical diseases and the Sustainable Development Goals.

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., Kenilworth, N.J., U.S.A.’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., Kenilworth, N.J., U.S.A., 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., Kenilworth, N.J., U.S.A. 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., Kenilworth, N.J., U.S.A.

For over 130 years, Merck & Co., Inc., Kenilworth, N.J., U.S.A., 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., Kenilworth, N.J., U.S.A. 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., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., 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 products that the products 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 2020 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).

¹ Sugiyama S et al. Real-world use of temsirolimus in Japanese patients with unresectable or metastatic renal cell carcinoma: recent consideration based on the results of a post-marketing, all-case surveillance study. *Japanese Journal of Clinical Oncology*, Volume 50, Issue 8, August 2020, Pages 940–947. <https://academic.oup.com/ijco/article/50/8/940/5847605>.

² Parada SA et al. Epidemiology of Renal Cell Carcinoma. *World J Oncol*. 2020 Jun; 11(3): 79–87. <https://www.wjon.org/index.php/wjon/article/view/1279/989>

³ James JH et al. Renal cell carcinoma. *Nat Rev Dis Primers*. 2017 Mar 9; 3: 17009. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5936048/pdf/nihms958498.pdf>.

⁴ 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>.

⁵ Gray RE et al. Renal Cell Carcinoma: Diagnosis and Management. *Am Fam Physician*. 2019 Feb 1;99(3):179-184. <https://www.aafp.org/afp/2019/0201/afp20190201p179.pdf>.

⁶ American Cancer Society, “Cancer Facts & Figures 2022.” <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf>.

⁷ Motzer R. et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *The New England Journal of Medicine*. <https://www.nejm.org/doi/pdf/10.1056/NEJMoa2035716?articleTools=true>.

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