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FDA Approves LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Combination for Patients With Certain Types of Advanced Endometrial Carcinoma

Immunotherapy and Tyrosine Kinase Inhibitor Combination 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

Study Results Demonstrated Statistically Significant Improvements in Overall Survival, Progression-Free Survival and Overall Response Rate, Helping to Address a Significant Unmet Need in Advanced Endometrial Carcinoma

TOKYO and KENILWORTH, N.J., July 22, 2021 – Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, “Eisai”) and Merck & Co., Inc., Kenilworth, N.J., U.S.A. (known as MSD outside the United States and Canada) today announced that the U.S. Food and Drug Administration (FDA) 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 the treatment of patients with 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.

The approval for this population is based on results from the pivotal Phase 3 Study 309/KEYNOTE-775 trial, in which LENVIMA plus KEYTRUDA demonstrated statistically significant improvements in overall survival (OS), reducing the risk of death by 32% (HR=0.68 [95% CI, 0.56-0.84]; p=0.0001), and progression-free survival (PFS), reducing the risk of disease progression or death by 40% (HR=0.60 [95% CI, 0.50-0.72]; p<0.0001), versus chemotherapy (investigator’s choice of doxorubicin or paclitaxel). LENVIMA plus KEYTRUDA also demonstrated statistically significant improvement in objective response rate (ORR), with an ORR of 30% (95% CI, 26-36) versus 15% (95% CI, 12-19) for patients who received investigator’s choice of

doxorubicin or paclitaxel, in addition to a complete response rate of 5% for KEYTRUDA plus LENVIMA versus 3% for doxorubicin or paclitaxel and a partial response rate of 25% versus 13%, respectively.

Adverse reactions, some of which can be serious or fatal, may occur with LENVIMA, including hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, renal failure or impairment, proteinuria, diarrhea, fistula formation and gastrointestinal perforation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impairment of thyroid stimulating hormone suppression/thyroid dysfunction, impaired wound healing and osteonecrosis of the jaw. Based on the type and/or severity of the adverse reaction, LENVIMA may be interrupted, reduced and/or discontinued. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception. For more information, see “Safety Information” below.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time during or after treatment with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, dermatologic reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of KEYTRUDA. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or permanently discontinued and corticosteroids administered if appropriate. KEYTRUDA can also cause severe or life-threatening infusion-related reactions. Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. For more information, see “Safety Information” below.

“With a five-year survival rate of just 17%, women with advanced endometrial cancer who are not candidates for curative therapy, particularly those with disease progression following prior systemic therapy have limited treatment options,” said Dr. Vicky Makker, principal investigator and medical oncologist, Memorial Sloan Kettering Cancer Center. “This approval is an important step forward in helping patients fight this difficult-to-treat malignancy, as physicians can now provide an option that may improve survival outcomes.”

“When compared to the chemotherapies used in this trial, this combination treatment regimen was proven to extend the lives of certain patients diagnosed with previously treated,

advanced endometrial cancer,” said Dr. Gregory Lubiniecki, Vice President, Oncology Clinical Research, Merck & Co., Inc., Kenilworth, N.J., U.S.A. Research Laboratories. “Based on Phase 3 data, today’s approval acts as the confirmatory trial to our previous accelerated approval of KEYTRUDA plus LENVIMA in patients with certain types of advanced endometrial cancer and reinforces the impact of our joint research with Eisai in exploring the potential of this combination to treat more patients with challenging types of cancer.”

“This FDA approval of LENVIMA plus KEYTRUDA for the treatment of patients with certain types of advanced endometrial cancer is an important step forward towards helping this patient community that has had limited treatment options,” said Dr. Takashi Owa, Chief Medicine Creation Officer and Chief Discovery Officer, Oncology Business Group at Eisai. “This marks a culmination of our relentless pursuit to address unmet needs of people with cancer, and we owe our deepest gratitude to those who participated in our Study 309/KEYNOTE-775 trial, their families and clinicians, and to our employees, whose collective commitment made this meaningful milestone possible.”

LENVIMA plus KEYTRUDA was previously approved under the FDA’s accelerated approval process, as well as under the agency’s Real-Time Oncology Review pilot program and its Project Orbis initiative, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation based on data from the Study 111/KEYNOTE-146 trial. In accordance with accelerated approval regulations, continued approval was contingent upon verification and description of clinical benefit; these accelerated approval requirements have been fulfilled with the data from Study 309/KEYNOTE-775.

Data Supporting the Approval

The approval was based on data from Study 309/KEYNOTE-775 ([ClinicalTrials.gov, NCT03517449](https://clinicaltrials.gov/ct2/show/study/NCT03517449)), a multicenter, open-label, randomized, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients with endometrial carcinoma that were not MSI-H or dMMR were stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomized (1:1) to one of the following treatment arms:

- LENVIMA (20 mg orally once daily) in combination with KEYTRUDA (200 mg intravenously [IV] every three weeks); or
- Investigator's choice, consisting of either doxorubicin (60 mg/m² every three weeks) or paclitaxel (80 mg/m² given weekly, three weeks on/one week off).

Treatment with LENVIMA plus KEYTRUDA continued until Response Evaluation Criteria in Solid Tumors (RECIST) v1.1-defined progression of disease as verified by blinded independent central review (BICR), unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit, and the treatment was tolerated. Assessment of tumor status was performed every eight weeks. The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of five target lesions per organ. Additional efficacy outcome measures included ORR and Duration of Response, as assessed by BICR.

Among the 697 not dMMR patients, 346 patients were randomized to LENVIMA plus KEYTRUDA, and 351 patients were randomized to investigator's choice of doxorubicin (n=254) or paclitaxel (n=97). The not dMMR population characteristics were: median age of 65 years (range: 30 to 86), 52% age 65 or older; 62% White, 22% Asian, and 3% Black; 60% ECOG PS of 0, and 40% ECOG PS of 1. The histologic subtypes were endometrioid carcinoma (55%), serous (30%), clear cell carcinoma (7%), mixed (4%), and other (3%). All 697 of these patients received prior systemic therapy for endometrial carcinoma: 67% had one, 30% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

Efficacy results for the not MSI-H or dMMR patients are summarized in the table below:

	Endometrial Carcinoma (not MSI-H or dMMR)	
Endpoint	LENVIMA and KEYTRUDA (KEYTRYDA 200 mg every 3 weeks) (n=346)	Doxorubicin or Paclitaxel (n=351)
OS		
Number (%) of patients with event	165 (48%)	203 (58%)
Median in months (95% CI)	17.4 (14.2, 19.9)	12.0 (10.8, 13.3)
Hazard ratio* (95% CI)	0.68 (0.56, 0.84)	
p-value [†]	0.0001	
PFS		
Number (%) of patients with event	247 (71%)	238 (68%)
Median in months (95% CI)	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)
Hazard ratio* (95% CI)	0.60 (0.50, 0.72)	

p-value [†]	<0.0001	
Objective Response Rate		
ORR [‡] (95% CI)	30% (26, 36)	15% (12, 19)
Complete response	5%	3%
Partial response	25%	13%
p-value [§]	<0.0001	
Duration of Response	n=105	n=53
Median in months (range)	9.2 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)
* Based on the stratified Cox regression model † Based on stratified log-rank test ‡ Response: Best objective response as confirmed complete response or partial response § Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation		

For patients with not MSI-H or dMMR status, the median duration of study treatment was 7.2 months (range: 1 day to 26.8 months) and the median duration of exposure to LENVIMA was 6.7 months (range: 1 day to 26.8 months). The median duration of exposure to KEYTRUDA was 6.8 months (range: 1 day to 25.8 months).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with LENVIMA plus KEYTRUDA, including two cases of pneumonia, and one of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving LENVIMA plus KEYTRUDA. Serious adverse reactions ($\geq 3\%$) were hypertension (4.4%) and urinary tract infections (3.2%).

Discontinuation of LENVIMA due to an adverse reaction (Grades 1-4) occurred in 26% of these patients. Discontinuation of KEYTRUDA due to an adverse reaction (Grades 1-4) occurred in 15% of these patients. The most common adverse reactions leading to discontinuation of LENVIMA ($\geq 1\%$) were hypertension (2.0%), asthenia (1.8%), diarrhea (1.2%), decreased appetite (1.2%), proteinuria (1.2%), and vomiting (1.2%). The most common adverse reaction leading to discontinuation of KEYTRUDA ($\geq 1\%$) was increased alanine aminotransferase (ALT) (1.2%).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 48% of these patients. The most common adverse reactions leading to interruption of LENVIMA ($\geq 2\%$) were hypertension (11%), diarrhea (11%), proteinuria (6%), decreased appetite (5%), vomiting (5%), increased ALT (3.5%), fatigue (3.5%), nausea (3.5%), abdominal pain (2.9%), decreased weight

(2.6%), urinary tract infection (2.6%), increased aspartate aminotransferase (AST) (2.3%), asthenia (2.3%), and palmar-plantar erythrodysesthesia (2.0%). The most common adverse reactions leading to interruption of KEYTRUDA ($\geq 3\%$) were diarrhea (8%), increased ALT (4.4%), increased AST (3.8%), and hypertension (3.5%).

Dose reductions of LENVIMA due to adverse events occurred in 67% of patients. The most common ($\geq 5\%$) adverse reactions resulting in dose reduction of LENVIMA were hypertension (18%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria (7%), fatigue (7%), decreased appetite (6%), asthenia (5%), and decreased weight (5%).

The most common adverse reactions of these patients (all grades $\geq 20\%$) for LENVIMA plus KEYTRUDA were hypothyroidism (67%), hypertension (67%), fatigue (58%), diarrhea (55%), musculoskeletal disorders (53%), nausea (49%), decreased appetite (44%), vomiting (37%), stomatitis (35%), decreased weight (34%), abdominal pain (34%), urinary tract infection (31%), proteinuria (29%), constipation (27%), headache (26%), hemorrhagic events (25%), palmar-plantar erythrodysesthesia (23%), dysphonia (22%), and rash (20%).

About Endometrial Cancer^{1,2,3,4,5}

Endometrial cancer begins in the inner lining of the uterus, which is known as the endometrium and is the most common type of cancer in the uterus. In 2020, it was estimated there were more than 417,000 new cases and more than 97,000 deaths from uterine body cancers worldwide (these estimates include both endometrial cancers and uterine sarcomas; more than 90% of uterine body cancers occur in the endometrium, so the actual numbers for endometrial cancer cases and deaths are slightly lower than these estimates). In Japan, there were more than 17,000 new cases of uterine body cancer and more than 3,000 deaths from the disease in 2020. In the U.S., it is estimated there will be more than 66,000 new cases of uterine body cancer and nearly 13,000 deaths from the disease in 2021. The five-year relative survival rate for metastatic endometrial cancer (stage IV) is estimated to be approximately 17%.

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 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 for advanced renal cell carcinoma following one prior antiangiogenic therapy. In Europe, the agent was launched under the brand name Kisplyx[®] for renal cell carcinoma. In the United States, it is approved in combination with KEYTRUDA (generic name: pembrolizumab) as a treatment for advanced endometrial carcinoma that is not MSI-H or dMMR who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. Based on the results of Study 111/KEYNOTE-146, it has been granted conditional approval for a similar indication in over 10 countries including Canada and Australia. In some regions, continued approval for this indication is contingent upon verification and description of clinical benefit in the confirmatory trials.

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 1,500 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.

Safety Information

For safety information on LENVIMA and KEYTRUDA in the United States, please visit the LENVIMA product website (<http://www.lenvima.com>), and KEYTRUDA product website (<https://www.keytruda.com>).

About the Merck & Co., Inc., Kenilworth, N.J., U.S.A. and Eisai 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 13 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), us.eisai.com (for U.S.) or www.eisai.eu (for Europe, Middle East, Africa), and connect with us on Twitter ([U.S.](#) and [global](#)) and [LinkedIn](#) (for U.S.).

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 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 American Cancer Society, Facts & Figures 2020 pdf:

<https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html>

² International Agency for Research on Cancer, World Health Organization. "Corpus uteri Fact Sheet." Cancer Today, 2020.

<https://gco.iarc.fr/today/data/factsheets/cancers/24-Corpus-uteri-fact-sheet.pdf>.

³ 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>.

⁴ Cancer Research Institute website, accessed 3/1/2021:

<https://www.cancerresearch.org/immunotherapy/cancer-types/uterine-endometrial-cancer>

⁵ American Cancer Society website, accessed 3/1/2021:

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

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