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**FDA Approves LENVIMA® (lenvatinib) plus KEYTRUDA® (pembrolizumab)  
Combination Treatment for Patients with Certain Types of Endometrial  
Carcinoma**

**Combination Treatment Approved for 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 and Are Not  
Candidates for Curative Surgery or Radiation**

**Under New FDA-Initiated Program, Combination Treatment Is the First to Receive  
Simultaneous Review Decisions in the U.S., Australia and Canada**

TOKYO, and KENILWORTH, N.J., [September 18, 2019] – Eisai (CEO: Haruo Naito) and Merck & Co., Inc., Kenilworth, N.J., U.S.A. (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) approved the combination of LENVIMA, the orally available kinase inhibitor discovered by Eisai, plus KEYTRUDA, Merck & Co., Inc., Kenilworth, N.J., U.S.A.'s anti-PD-1 therapy, 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 and are not candidates for curative surgery or radiation. This marks the first U.S. approval for the combination of LENVIMA plus KEYTRUDA and the first time an anti-PD-1 therapy is approved in combination with a kinase inhibitor for advanced endometrial carcinoma in the U.S. Following submission on June 17, this is an accelerated approval reviewed under the FDA's Real-Time Oncology Review (RTOR) pilot program, which aims to improve the efficiency of the review process for applications to ensure that treatments are available to patients as early as possible. RTOR allows the FDA to review much of the data earlier, before the applicant formally submits the complete application. This accelerated approval is based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial. According to the FDA, this review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for

concurrent submission and review of oncology drugs among its international partners. Under this project, the FDA, the Australian Therapeutic Goods Administration (TGA) and Health Canada collaboratively reviewed applications for two oncology drugs, allowing for simultaneous decisions in all three countries.

The approval was based on data from Study 111/KEYNOTE-146, a Phase 2, multi-cohort, multi-center, open-label, single-arm trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. In the 94 patients with tumors that were not MSI-H or dMMR, the LENVIMA plus KEYTRUDA combination demonstrated an ORR of 38.3% (95% CI, 29-49), with a complete response rate of 10.6% (n=10) and a partial response rate of 27.7% (n=26). In the patients who had a response as determined by independent review (n=36), at the time of data cutoff, the median DOR was not reached (range, 1.2+ to 33.1+months), and 69% of these patients experienced responses lasting six months or longer. The most common adverse reactions ( $\geq 20\%$ ) with the LENVIMA plus KEYTRUDA combination were fatigue, musculoskeletal pain, hypertension, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough and rash.

“When diagnosed early, endometrial carcinoma can have a good prognosis; however, for women whose cancer has progressed following prior systemic therapy, there are few FDA-approved treatment options,” said Dr. Vicky Makker, medical oncologist, Memorial Sloan Kettering Cancer Center. “Based on objective response rate and the duration of response, this approval of the LENVIMA plus KEYTRUDA combination will help address a significant unmet medical need for 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.”

“Today’s approval of the LENVIMA plus KEYTRUDA combination for advanced endometrial carcinoma that has progressed following prior systemic therapy brings the first approved combination treatment to women with this type of cancer whose tumors are not MSI-H or dMMR and who are not candidates for curative surgery or radiation, and this demonstrates the potential of our collaboration with Eisai,” said Dr. Jonathan Cheng, Vice President, Oncology Clinical Research, Merck & Co., Inc., Kenilworth, N.J., U.S.A. Research Laboratories. “Merck &

Co., Inc., Kenilworth, N.J., U.S.A. is committed to developing this combination through the LEAP (LEnvatinib And Pembrolizumab) clinical program, which is under active investigation.”

“At least 75% of endometrial cancer cases are not microsatellite instability-high or mismatch repair deficient, and these women have been in need of new treatment options,” said Dr. Takashi Owa, Vice President, Chief Medicine Creation and Chief Discovery Officer, Oncology Business Group at Eisai. “We are very pleased that the LENVIMA plus KEYTRUDA combination for 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 has been selected for FDA’s RTOR pilot program, launched last year, and has been approved approximately three months after the submission. We look forward to providing this combination therapy to women with certain types of advanced endometrial carcinoma.”

### **Data Supporting the Approval**

The approval was based on data from Study 111/KEYNOTE-146, a Phase 2, multi-cohort, multicenter, open-label, single-arm trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were treated with KEYTRUDA 200 mg intravenously every three weeks in combination with LENVIMA 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator.

Administration of KEYTRUDA plus LENVIMA was permitted beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA dosing was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every six weeks until week 24, followed by every nine weeks thereafter. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) by independent radiologic review committee (IRC) using RECIST 1.1.

Among the 108 patients, 87% (n=94) had tumors that were not MSI-H or dMMR, 10% (n=11) had tumors that were MSI-H or dMMR, and 3% (n=3) had tumors that had unknown status. The baseline characteristics of the 94 patients with tumors that were not MSI-H or dMMR were: median age of 66 years, with 62% age 65 or older; and 86% White, 6% Black, 4% Asian,

and 3% other races. All 94 patients had received prior systemic therapy for endometrial carcinoma; 51% had one, 38% had two, and 11% had three or more prior systemic therapies.

In the 94 patients with tumors that were not MSI-H or dMMR, the LENVIMA plus KEYTRUDA combination demonstrated an ORR of 38.3% (95% CI, 29%-49%), with a complete response rate of 10.6% (n=10) and a partial response rate of 27.7% (n=26). The median follow-up time was 18.7 months. In the patients who had a response as determined by independent review (n=36), at the time of data cutoff the median DOR was not reached (range, 1.2+ to 33.1+ months), and 69% of these patients experienced responses lasting six months or greater.

The median duration of study treatment was seven months (range; 0.03 to 37.8 months), and the median duration of exposure to KEYTRUDA was six months (range; 0.03 to 23.8 months). Fatal adverse reactions occurred in 3% of patients treated with LENVIMA plus KEYTRUDA, including gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS) with intraventricular hemorrhage, and intracranial hemorrhage. Serious adverse reactions occurred in 52% of patients receiving LENVIMA plus KEYTRUDA. The most common serious adverse reactions ( $\geq 3\%$ ) with the LENVIMA plus KEYTRUDA combination were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage, fatigue, nausea, confusional state, pleural effusion (4% each), adrenal insufficiency, colitis, dyspnea and pyrexia (3% each).

In this study, permanent discontinuation due to adverse reactions (Grade 1-4) occurred in 21% of patients who received LENVIMA plus KEYTRUDA. KEYTRUDA was discontinued due to adverse reactions (Grade 1-4) in 19% of patients, regardless of action taken with LENVIMA. The most common adverse reactions ( $\geq 2\%$ ) leading to discontinuation of KEYTRUDA were adrenal insufficiency, colitis, pancreatitis and muscular weakness (2% each). Adverse reactions leading to interruption of KEYTRUDA occurred in 49% of patients. The most common adverse reactions leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were fatigue (14%), diarrhea, and decreased appetite (6% each), rash (5%), renal impairment, vomiting, increased lipase, and decreased weight (4% each), nausea, increased blood alkaline phosphatase, and skin ulcer (3% each), adrenal insufficiency, increased amylase, hypocalcemia, hypomagnesemia, hyponatremia, peripheral edema, musculoskeletal pain, pancreatitis, and syncope (2% each). Adverse reactions led to dose reduction or interruption in 88% of patients receiving LENVIMA. The most common adverse reactions ( $\geq 5\%$ ) resulting in dose reduction or interruption of LENVIMA were fatigue (32%), hypertension (26%), diarrhea (18%), nausea, palmar-plantar erythrodysesthesia, and vomiting (13% each), decreased appetite (12%), musculoskeletal pain

(11%), stomatitis (9%), abdominal pain, hemorrhages (7% each), renal impairment, decreased weight (6% each), rash, headache, increased lipase, and proteinuria (5% each).

The most common adverse reactions ( $\geq 20\%$ ) with LENVIMA plus KEYTRUDA treated patients were fatigue, musculoskeletal pain, and hypertension (65% each), diarrhea (64%), decreased appetite (52%), hypothyroidism (51%), nausea (48%), stomatitis (43%), vomiting (39%), decreased weight (36%), abdominal pain, and headache (33% each), constipation (32%), urinary tract infection (31%), dysphonia (29%), hemorrhagic events (28%), hypomagnesemia (27%), palmar-plantar erythrodysesthesia syndrome (26%), dyspnea (24%), cough and rash (21% each).

### **Recommended Dosage for Endometrial Carcinoma**

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every three weeks in combination with LENVIMA 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression. Refer to the LENVIMA prescribing information for recommended dosing information, as appropriate.

### **About LENVIMA® (lenvatinib) Capsules**

LENVIMA, discovered and developed by Eisai, is a 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 $\alpha$ ), KIT, and RET. In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages population, increased activated cytotoxic T cells population, 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 55 countries including Japan, the United States, in Europe and Asia, and for hepatocellular carcinoma in over 50 countries including Japan, the United States, in Europe, China and in Asia. Additionally, it is also approved in combination with everolimus as a treatment for renal cell carcinoma (second-line) in over 50 countries, including the United States and in Europe. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma.

### **About KEYTRUDA® (pembrolizumab) Injection**

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., Kenilworth, N.J., U.S.A. has the industry's largest immuno-oncology clinical research program. There are currently more than 1,000 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 Merck & Co., Inc., Kenilworth, N.J., U.S.A.'s anti-PD-1 therapy KEYTRUDA.

In addition to ongoing clinical studies evaluating the KEYTRUDA plus LENVIMA combination across several different tumor types, the companies will jointly initiate new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program, which will evaluate the combination to support 11 potential indications in six types of cancer. The LEAP clinical program also includes a new basket trial targeting six additional cancer types.

The pivotal studies evaluating the combination therapy of LENVIMA plus KEYTRUDA in hepatocellular carcinoma (first-line), renal cell carcinoma (first-line), melanoma (first-line and second-line), non-squamous cell lung carcinoma (first-line [all-comer], first-line [PD-L1 positive] and second-line), endometrial carcinoma (first-line and second-line), and bladder carcinoma (first-line) are currently underway.

### **Eisai's Focus on Cancer**

Eisai focuses on the development of anticancer drugs, targeting the tumor microenvironment with experience and knowledge from Halaven and Lenvima 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 become a frontrunner in oncology area. Eisai will discover innovative new drug with new target and mechanism of action from these Ricchi, and aims for contribution to cure 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](http://www.eisai.com) (for global), [us.eisai.com](http://us.eisai.com) (for U.S.) or [www.eisai.co.uk](http://www.eisai.co.uk) (for U.K.), 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](http://www.merck.com/clinicaltrials).

### **About Merck & Co., Inc., Kenilworth, N.J., U.S.A.**

For more than a century, Merck & Co., Inc., Kenilworth, N.J., U.S.A., a leading global biopharmaceutical company 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. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to 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 advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit [www.merck.com](http://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 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 2018 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 (<http://www.sec.gov>).

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