

**Eisai Co., Ltd.**  
**Public Relations:**  
+81-(0)3-3817-5120

**Merck & Co., Inc., Kenilworth, N.J., U.S.A.**  
**Media Relations**  
Patrick Ryan: (973) 275-7075  
Rebecca Newberry: (484) 678-2952

**Eisai Co., Ltd.**  
**Investor Relations:**  
+81-(0)3-3817-3016

**Merck & Co., Inc., Kenilworth, N.J., U.S.A.**  
**Investor Relations**  
Peter Dannenbaum: (908) 740-1037  
Courtney Ronaldo: (908) 740-6132

**LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Significantly Improved Progression-Free Survival and Overall Survival Versus Chemotherapy in Patients With Advanced Endometrial Cancer Following Prior Platinum-Based Chemotherapy in Phase 3 Study**

***LENVIMA Plus KEYTRUDA Significantly Reduced the Risk of Death by 38%, With a Median Overall Survival of 18.3 Months Versus 11.4 Months With Chemotherapy Regardless of Mismatch Repair Status***

***First Results From Pivotal Study 309/KEYNOTE-775 Trial Presented at Society of Gynecologic Oncology (SGO) 2021 Annual Meeting on Women's Cancer***

TOKYO and KENILWORTH, N.J., March 19, 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 the first presentation of investigational data from the pivotal Phase 3 Study 309/KEYNOTE-775 trial in an oral plenary session (Plenary Session #10191) at the virtual Society of Gynecologic Oncology (SGO) 2021 Annual Meeting on Women's Cancer. The trial evaluated 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 certain patients with advanced, metastatic or recurrent endometrial cancer following one prior platinum-based regimen in any setting.

The study met the dual primary endpoints of progression-free survival (PFS), as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, overall survival (OS), as well as the secondary efficacy endpoint of objective response rate (ORR), as assessed by BICR per RECIST v1.1, in the all-comer population (mismatch repair proficient [pMMR] and mismatch repair deficient [dMMR]) and in the pMMR subgroup. Median follow-up was 11.4 months for both the all-comer population and pMMR subgroup. A statistically significant and clinically meaningful improvement in PFS was seen in the

all-comer population, in which LENVIMA plus KEYTRUDA (n=411) reduced the risk of disease progression or death by 44% (HR=0.56 [95% CI: 0.47-0.66]; p<0.0001), with a median PFS of 7.2 months (95% CI: 5.7-7.6; number of events=281) versus 3.8 months (95% CI: 3.6-4.2; number of events=286) for patients who received chemotherapy (treatment of physician's choice [TPC] of doxorubicin or paclitaxel; n=416). Additionally, a statistically significant and clinically meaningful improvement in OS was seen in the all-comer population, in which LENVIMA plus KEYTRUDA reduced the risk of death by 38% (HR=0.62 [95% CI: 0.51-0.75]; p<0.0001), with a median OS of 18.3 months (95% CI: 15.2-20.5; number of events=188) versus 11.4 months (95% CI: 10.5-12.9; number of events=245) for patients who received TPC. The safety profile of LENVIMA plus KEYTRUDA was generally consistent with the established safety profiles of the individual monotherapies.

“Patients diagnosed with endometrial cancer, the most common type of gynecologic cancer in the U.S., face low survival rates when diagnosed at an advanced stage or at recurrence, especially once the disease progresses after prior platinum-based therapy and is not amenable to curative surgery or radiation,” said Dr. Vicky Makker, Principal Investigator and Medical Oncologist, Memorial Sloan Kettering Cancer Center. “With a 38% reduction in risk of death regardless of mismatch repair status, LENVIMA plus KEYTRUDA significantly improved overall survival compared with chemotherapy in the all-comer group of patients with advanced, metastatic or recurrent endometrial carcinoma, which is very encouraging, as this arm included an investigational patient population for which more data have been sought after by the gynecologic oncology community.”

In the all-comer population, the secondary efficacy endpoint of ORR was 31.9% (95% CI: 27.4-36.6), with a complete response (CR) rate of 6.6% and a partial response (PR) rate of 25.3%, for patients who received LENVIMA plus KEYTRUDA versus 14.7% (95% CI: 11.4-18.4), with a CR rate of 2.6% and a PR rate of 12.0% for patients who received TPC (ORR difference versus TPC: 17.2 percentage points; p<0.0001). For patients who responded, the median duration of response (DOR) was 14.4 months (range: 1.6-23.7) for patients who received LENVIMA plus KEYTRUDA versus 5.7 months (range: 0.0-24.2) for patients who received TPC.

“In this confirmatory Phase 3 study, KEYTRUDA plus LENVIMA demonstrated statistically significant improvements in progression-free survival, overall survival and objective response rate versus chemotherapy,” said Dr. Gregory Lubiniecki, Vice President, Oncology Clinical Research,

Merck & Co., Inc., Kenilworth, N.J., U.S.A. Research Laboratories. “We are encouraged by these results that reaffirm the companies’ commitment to explore the potential of the combination to help more patients with difficult-to-treat types of cancer.”

“The positive results seen in Study 309/KEYNOTE-775 help confirm the currently approved use of the LENVIMA plus KEYTRUDA combination in certain patients with advanced endometrial carcinoma,” said Dr. Takashi Owa, Chief Medicine Creation Officer and Chief Discovery Officer, Oncology Business Group at Eisai. “As this stage of disease has been notoriously difficult to treat, the companies remain committed to addressing the unmet need of advanced endometrial carcinoma. We are grateful to the patients and health care providers whose participation and persistence amid a global pandemic have made this milestone possible.”

Results were similar across the all-comer population and the pMMR subgroup. In the pMMR subgroup, LENVIMA plus KEYTRUDA reduced the risk of disease progression or death by 40% (HR=0.60 [95% CI: 0.50-0.72]; p<0.0001), with a median PFS of 6.6 months (95% CI: 5.6-7.4; number of events=247) versus 3.8 months (95% CI: 3.6-5.0; number of events=238) for patients who received TPC. LENVIMA plus KEYTRUDA reduced the risk of death by 32% (HR=0.68 [95% CI: 0.56-0.84]; p =0.0001), with a median OS of 17.4 months (95% CI: 14.2-19.9; number of events=165) versus 12.0 months (95% CI: 10.8-13.3; number of events=203) for patients who received TPC. The secondary endpoint of ORR was 30.3% (95% CI: 25.5-35.5), with a CR rate of 5.2% and a PR rate of 25.1%, for patients who received LENVIMA plus KEYTRUDA versus 15.1% (95% CI: 11.5-19.3), with a CR rate of 2.6% and a PR rate of 12.5%, for patients who received TPC (ORR difference versus TPC: 15.2 percentage points: p<0.0001). For patients who responded, the median DOR was 9.2 months (range: 1.6-23.7) for patients who received LENVIMA plus KEYTRUDA versus 5.7 months (range: 0.0-24.2) for patients who received TPC.

In the all-comer population, in the LENVIMA plus KEYTRUDA arm (n=406), any grade treatment-emergent adverse events (TEAEs) led to discontinuation of LENVIMA in 30.8% of patients, of KEYTRUDA in 18.7% of patients, and of both in 14.0% of patients. In the TPC arm (n=388), any grade TEAEs led to discontinuation of chemotherapy in 8.0% of patients. Grade 5 TEAEs of any cause occurred in 5.7% of patients in the LENVIMA plus KEYTRUDA arm and in 4.9% of patients in the TPC arm. Grade ≥3 TEAEs occurred in 88.9% of patients in the LENVIMA plus KEYTRUDA arm and in 72.7% of patients in the TPC arm. In the LENVIMA plus KEYTRUDA

arm, the most common TEAEs of any grade occurring in at least 25% of patients were hypertension (64.0%), hypothyroidism (57.4%), diarrhea (54.2%), nausea (49.5%), decreased appetite (44.8%), vomiting (36.7%), weight decrease (34.0%), fatigue (33.0%), arthralgia (30.5%), proteinuria (28.8%), anemia (26.1%), constipation (25.9%), and urinary tract infection (25.6%). In the TPC arm, the most common TEAEs of any grade occurring in at least 25% of patients were anemia (48.7%), nausea (46.1%), neutropenia (33.8%), alopecia (30.9%), and fatigue (27.6%). Median treatment duration was 231 days (range: 1-817) with LENVIMA plus KEYTRUDA and 104.5 days (range: 1-785) with TPC.

Study 309/KEYNOTE-775 is the confirmatory trial for Study 111/KEYNOTE-146, which supported the U.S. Food and Drug Administration's (FDA) 2019 accelerated approval of the LENVIMA plus KEYTRUDA combination 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.

### **Study 309/KEYNOTE-775 Trial Design (Plenary Session #10191)**

Study 309/KEYNOTE-775 is a multicenter, randomized, open-label, Phase 3 trial (ClinicalTrials.gov, [NCT03517449](https://clinicaltrials.gov/ct2/show/study/NCT03517449)) evaluating LENVIMA in combination with KEYTRUDA in patients with advanced endometrial cancer following one prior platinum-based regimen in any setting. The dual primary endpoints are PFS, as assessed by BICR per RECIST v1.1, and OS. Select secondary endpoints include ORR by BICR per RECIST v1.1 and safety/tolerability. Of the 827 patients enrolled, 697 patients had tumors that were pMMR, and 130 patients had tumors that were dMMR. Patients were randomized 1:1 to receive LENVIMA (20 mg orally once daily) in combination with KEYTRUDA (200 mg intravenously [IV] every three weeks) for up to 35 cycles (approximately two years); or chemotherapy treatment of physician's choice (TPC) of either doxorubicin 60 mg/m<sup>2</sup> IV every three weeks for up to a maximum cumulative dose of 500 mg/m<sup>2</sup> or paclitaxel 80 mg/m<sup>2</sup> IV on a 28-day cycle [three weeks of receiving weekly paclitaxel and one week of not receiving paclitaxel]).

### **About Endometrial Cancer<sup>1,2,3,4,5</sup>**

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 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 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, 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 70 countries including Japan, in Europe, China and in Asia, and in the U.S. for radioiodine-refractory differentiated thyroid cancer. In addition, Lenvima has been approved for monotherapy as a treatment for unresectable hepatocellular carcinoma in over 65 countries including Japan, the United States, in Europe, China and in Asia. It is also approved in combination with everolimus as a treatment for renal cell carcinoma following prior antiangiogenic therapy in over 60 countries, including the United States, in Europe and Asia. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma. In addition, it is approved in combination with KEYTRUDA as a treatment for advanced endometrial cancer 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 in over 10 countries including the United States, Canada and Australia. 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-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 1,400 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 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 14 different tumor types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial cancer, biliary tract cancer, colorectal cancer, gastric cancer, glioblastoma, ovarian cancer, pancreatic cancer and triple-negative breast cancer) 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](http://www.eisai.com) (for global), [us.eisai.com](http://us.eisai.com) (for U.S.) or [www.eisai.eu](http://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](http://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](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 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](http://www.sec.gov)).

<sup>1</sup> American Cancer Society, Facts & Figures 2020 pdf:

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

<sup>2</sup> 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> .

<sup>3</sup> 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> .

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

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



<sup>5</sup> 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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