FOR IMMEDIATE RELEASE
April 23, 2021

Eisai Co., Ltd.
MSD K.K.

APPLICATION SUBMITTED FOR ADDITIONAL INDICATION OF ANTI CANCER AGENT LENVIMA® IN COMBINATION WITH KEYTRUDA® AS A TREATMENT FOR ADVANCED UTERINE BODY CANCER IN JAPAN

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and MSD K.K. (Headquarters: Tokyo, President: Kyle Tattle, "MSD"), a subsidiary of Merck & Co., Inc., Kenilworth, N.J., U.S.A., (known as MSD outside the United States and Canada) announced today an application submission in Japan for the additional indication of Eisai's in-house discovered and developed multiple receptor tyrosine kinase inhibitor, LENVIMA® (generic name: lenvatinib mesylate), in combination with Merck & Co., Inc., Kenilworth, N.J., U.S.A.'s KEYTRUDA® (generic name: pembrolizumab) as a treatment for patients with advanced uterine body cancer.

This application is based on the results of the pivotal Phase 3 Study 309/KEYNOTE-775 for the treatment of patients with advanced endometrial carcinoma (advanced uterine body cancer in Japan), following at least one prior platinum-based regimen, which were presented at the Society of Gynecologic Oncology (SGO) 2021 Annual Meeting on Women's Cancer in March 2021. In this trial, LENVIMA plus KEYTRUDA demonstrated a statistically significant and clinically meaningful improvement in the primary endpoints of Progression-Free Survival (PFS) and Overall Survival (OS) as well as the secondary endpoint of Objective Response Rate (ORR) versus chemotherapy (treatment of physician's choice of doxorubicin or paclitaxel). The safety profile of LENVIMA plus KEYTRUDA was consistent with previously reported studies.

LENVIMA plus KEYTRUDA has received orphan drug designation for a prospective indication for uterine body cancer by the Ministry of Health, Labour and Welfare, Japan (MHLW). Under this system, this application will be subject to priority review.

It is estimated that there were more than 417,000 new cases of uterine body cancer diagnosed worldwide and nearly 97,000 deaths from the disease in 2020.[1] In Japan, there were more than 17,000 new cases and more than 3,000 deaths in 2020.[2] Endometrial carcinoma is the most common type of uterine body cancer. It is considered that more than 90% of uterine body cancers occur in the endometrium.[3] Survival is highly dependent on the stage at diagnosis, and with a five-year survival rate of 17% for metastatic disease, the prognosis for these patients is poor.[4]

Eisai and MSD have been collaborating through the provision of information on LENVIMA in Japan since October 2018, and will work together to expedite the maximization of contribution by the LENVIMA plus KEYTRUDA combination therapy to patients with cancer.

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<Notes to editors>

1. About LENVIMA (generic name: lenvatinib mesylate)

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 (PDGFRα), 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 70 countries including Japan, in Europe, China and in Asia, and in the United States 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 (generic name: pembrolizumab) 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. Lenvima has also been approved for monotherapy as a treatment for unresectable thymic carcinoma in Japan.

2. About KEYTRUDA (pembrolizumab)

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. (known as MSD outside the United States and Canada) 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.

In Japan, KEYTRUDA has been approved for the treatment of melanoma, unresectable advanced/recurrent non-small cell lung cancer, relapsed or refractory classical Hodgkin lymphoma, radically unresectable urothelial carcinoma that have progressed after chemotherapy, advanced/recurrent microsatellite instability-high (MSI-High) solid tumors that have progressed after chemotherapy (limited to use when difficult to treat with standard of care), radically unresectable or metastatic renal cell carcinoma, recurrent or distant metastatic head and neck cancer, and PD-L1-positive radically unresectable advanced/recurrent esophageal squamous cell carcinoma that have progressed after chemotherapy.

3. About Study 309/KEYNOTE-775

Study 309/KEYNOTE-775 is a multicenter, randomized, open-label, Phase 3 trial (ClinicalTrials.gov, NCT03517449) evaluating LENVIMA in combination with KEYTRUDA in patients with advanced endometrial carcinoma (advanced uterine body cancer in Japan) following at least one prior platinum-based regimen. The dual primary endpoints are PFS, as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (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 mismatch repair proficient (pMMR), and 130 patients had tumors that were mismatch repair deficient (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^2 IV every three weeks for up to a maximum cumulative dose of 500 mg/m^2 or paclitaxel 80 mg/m^2 IV on a 28-day cycle [three weeks of receiving weekly paclitaxel and one week of not receiving paclitaxel]).

The study met the dual primary endpoints of PFS, as assessed by BICR per RECIST v1.1, OS, as well as the secondary efficacy endpoint of ORR, as assessed by BICR per RECIST v1.1, in the all-comer population (pMMR and 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 TPC (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.

In the all-comer population, the secondary efficacy endpoint of ORR was 31.9% (95% CI: 27.4-36.6), with a CR rate of 6.6% and a 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.

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.

4. 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., 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 a 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 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.

5. About Eisai Co., Ltd.

Eisai is a leading global research and development-based pharmaceutical company headquartered in Japan, with approximately 10,000 employees worldwide. Eisai defines 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*, Eisai takes 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.).

6. About MSD

For 130 years, MSD 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. MSD is a trade name of Merck & Co., Inc., with headquarters in Kenilworth, N.J., U.S.A. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, MSD 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.msd.co.jp and connect with us on Facebook, Twitter and YouTube.

[1]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
[2]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
[3]2017 Patient Survey, Official Statistics of Japan (e-Stat) https://www.e-stat.go.jp/ (available in Japanese only).
[4]American Cancer Society, "CANCER FACT & FIGURES 2020." https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf

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