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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 RENAL CELL CARCINOMA 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 that Eisai has submitted an application in Japan for the additional indication of its 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 renal cell carcinoma (RCC). This is the first application to be submitted in Japan for this combination therapy.

This application is based on the results of the Phase 3 CLEAR study (Study 307/KEYNOTE-581) for the first-line treatment of patients with advanced RCC, which were presented at the 2021 Genitourinary Cancers Symposium (ASCO GU), and simultaneously published in the *New England Journal of Medicine* in February 2021. In this trial, LENVIMA plus KEYTRUDA demonstrated statistically significant and clinically meaningful improvements in the primary endpoint of progression-free survival (PFS) as well as key secondary endpoints of overall survival (OS) and objective response rate (ORR) versus sunitinib. The safety profile of LENVIMA plus KEYTRUDA was consistent with previously reported studies.

Worldwide, it is estimated that there were more than 430,000 new cases of kidney cancer diagnosed and nearly 180,000 deaths from the disease in 2020.[1] In Japan, there were more than 25,000 new cases and 8,000 deaths in 2020.[2] RCC is by far the most common type of kidney cancer; about nine out of 10 kidney cancers are RCC.[3] Most cases of RCC are discovered incidentally during imaging tests for other abdominal diseases. Approximately 30% of patients with RCC will have metastatic disease at diagnosis, and as many as 40% will develop metastases after primary surgical treatment for localized RCC.[4,5] Survival is highly dependent on the stage at diagnosis, and with a five-year survival rate of 12% for metastatic disease, the prognosis for these patients is poor.[6]

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 LENVIMA and KEYTRUDA 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, 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 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 Renal Cell Carcinoma (RCC)

Worldwide, it is estimated there were more than 430,000 new cases of kidney cancer diagnosed and nearly 180,000 deaths from the disease in 2020.[1] In Japan, there were more than 25,000 new cases and 8,000 deaths in 2020.[2] In the U.S. alone, it is estimated there will be more than 76,000 new cases of kidney cancer diagnosed and nearly 14,000

deaths from the disease in 2021.[3] RCC is by far the most common type of kidney cancer; about nine out of 10 kidney cancers are RCCs.[3] RCC is about twice as common in men as in women.[3] Most cases of RCC are discovered incidentally during imaging tests for other abdominal diseases. Approximately 30% of patients with RCC will have metastatic disease at diagnosis, and as many as 40% will develop metastases after primary surgical treatment for localized RCC.[4,5] Survival is highly dependent on the stage at diagnosis, and with a five-year survival rate of 12% for metastatic disease, the prognosis for these patients is poor.[6]

4. About the CLEAR Study (Study 307/KEYNOTE-581)

The CLEAR Study (Study 307/KEYNOTE-581) is a Phase 3, multi-center, randomized, open-label trial (ClinicalTrials.gov, NCT02811861) evaluating LENVIMA in combination with KEYTRUDA or in combination with everolimus versus sunitinib for the first-line treatment of patients with advanced RCC. The primary endpoint is PFS by independent review per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Key secondary endpoints include OS, ORR and safety. A total of 1,069 patients were randomized to one of three treatment arms to receive LENVIMA (20 mg orally once daily) in combination with KEYTRUDA (200 mg intravenously every three weeks); or LENVIMA (18 mg orally once daily) in combination with everolimus (5 mg orally once daily); or sunitinib (50 mg orally once daily for four weeks on treatment, followed by two weeks off treatment).

In the trial's primary endpoint of PFS, as assessed by independent review per RECIST v1.1, LENVIMA plus KEYTRUDA reduced the risk of disease progression or death by 61% (HR=0.39 [95% CI: 0.32-0.49]; p<0.001), with a median PFS of 23.9 months (95% CI: 20.8-27.7) versus 9.2 months (95% CI: 6.0-11.0) for patients who received sunitinib. In the trial's key secondary endpoints, LENVIMA plus KEYTRUDA reduced the risk of death by 34% (HR=0.66 [95% CI: 0.49-0.88]; p=0.005) versus patients who received sunitinib. Median OS was not reached in either treatment arm after a median follow-up of 27 months. Treatment with LENVIMA plus KEYTRUDA resulted in an ORR of 71.0% (95% CI: 66.3-75.7), with a complete response (CR) rate of 16.1% and a partial response (PR) rate of 54.9%, versus an ORR of 36.1% (95% CI: 31.2-41.1), with a CR rate of 4.2% and a PR rate of 31.9%, for patients who received sunitinib (relative risk=1.97 [95% CI: 1.69-2.29]). Median duration of response (DOR) for patients who received LENVIMA plus KEYTRUDA was 25.8 months (95% CI: 22.1-27.9) versus 14.6 months (95% CI: 9.4-16.7) for patients who received sunitinib.

In the LENVIMA plus KEYTRUDA arm, treatment-related adverse events (TRAEs) led to discontinuation of LENVIMA in 18.5% of patients, of KEYTRUDA in 25.0% of patients, and of both in 9.7% of patients. In the sunitinib arm, TRAEs led to discontinuation of sunitinib in 10.0% of patients. Grade 5 TRAEs occurred in 1.1% of patients in the LENVIMA plus KEYTRUDA arm versus 0.3% of patients in the sunitinib arm. Grade ≥3 TRAEs occurred in 71.6% of patients in the LENVIMA plus KEYTRUDA arm versus 58.8% of patients in the sunitinib arm. The most common TRAEs of any grade occurring in at least 20% of patients in the LENVIMA plus KEYTRUDA arm were diarrhea (54.5%), hypertension (52.3%), hypothyroidism (42.6%), decreased appetite (34.9%), fatigue (32.1%) and stomatitis (32.1%). In the sunitinib arm, the most common TRAEs of any grade occurring in at least 20% of patients were diarrhea (44.4%), hypertension (39.1%), stomatitis (37.4%), hand-foot syndrome (35.9%), fatigue (32.1%) and nausea (27.6%).

5. 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.

6. 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.).

7. 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.

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