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Eisai and Merck & Co., Inc., Kenilworth, N.J., USA. Receive Breakthrough Therapy Designation from U.S. FDA for LENVIMA[®] (lenvatinib mesylate) and KEYTRUDA[®] (pembrolizumab) as Combination Therapy for Advanced and/or Metastatic Renal Cell Carcinoma

Tokyo, Japan and Kenilworth, NJ – January 9, 2018 – Eisai Co., Ltd. and Merck & Co., Inc. Kenilworth, N.J., USA (NYSE:MRK) (known as MSD outside the United States and Canada), announced today that they received Breakthrough Therapy Designation from the U.S. Food and Drug Administration (FDA) for Eisai's multiple receptor tyrosine kinase inhibitor LENVIMA[®] (generic name: lenvatinib mesylate) in combination with MSD's anti-PD-1 therapy KEYTRUDA[®] (generic name: pembrolizumab) for the potential treatment of patients with advanced and/or metastatic renal cell carcinoma. The LENVIMA and KEYTRUDA combination therapy is being jointly developed by Eisai and MSD. This is the second Breakthrough Therapy Designation for LENVIMA and the twelfth Breakthrough Therapy Designation granted to KEYTRUDA.

The Breakthrough Therapy Designation is a U.S. FDA program intended to expedite development and review of drugs for serious or life-threatening conditions. In order to qualify for this designation, preliminary clinical evidence must demonstrate that the drug may provide substantial improvement over currently available therapy on at least one clinically significant endpoint. The benefits of this Breakthrough Therapy Designation include more intensive guidance on an efficient drug development program, access to a regulatory liaison to help accelerate review time, and eligibility for rolling review as well as priority review.

This Breakthrough Therapy Designation was based on the results of the renal cell carcinoma cohort in Study 111,¹ a multicenter, open-label Phase Ib/II clinical study being carried out in the United States and the European Union to evaluate the efficacy and safety of LENVIMA in combination with KEYTRUDA in subjects with selected solid tumors.

Dr. Takashi Owa, Chief Medicine Creation Officer, Oncology Business Group, Eisai Co., Ltd., commented: "We are encouraged that the FDA has recognized the potential of LENVIMA plus KEYTRUDA for patients with advanced and/or metastatic renal cell carcinoma with the Breakthrough Therapy Designation. As a human health care company dedicated to giving our first thought to patients, we are committed to working closely with MSD and the FDA to expedite this clinical program with the hope that we may offer another important option for patients in need."

"The FDA's Breakthrough Therapy Designation for the LENVIMA and KEYTRUDA combination in advanced and/or metastatic renal cell carcinoma provides us with the opportunity to accelerate our effort to bring an important potential treatment option to these patients," said Dr. Roy Baynes, Senior Vice President and Head of Global Clinical Development, Chief Medical Officer, MSD Research Laboratories. "We remain committed to understanding the full potential of KEYTRUDA across cancers and treatment



settings, and our collaboration with Eisai is one of the many ways we are executing on this commitment to helping more patients.”

About Study 111

Study 111 is a multicenter, open-label Phase Ib/II clinical study being carried out in the United States and European Union to evaluate the efficacy and safety of LENVIMA in combination with KEYTRUDA. The primary objective of the Phase Ib part was to determine the maximum tolerated dose. Patients with unresectable solid tumors (renal cell carcinoma, endometrial cancer, non-small cell lung cancer, urothelial cancer, squamous cell, head and neck cancer, and melanoma) who had progressed after treatment with approved therapies or for which there are no standard effective therapies available were administered 24 mg of LENVIMA orally daily, as well as 200 mg of KEYTRUDA intravenously every three weeks. Dose reductions of LENVIMA were permitted based on observed toxicity. The Phase II part was conducted on patients who had select solid tumors with 0-2 prior lines of systemic therapy (unless discussed with the sponsor) with a recommended dosage of 20 mg of LENVIMA daily and 200 mg of KEYTRUDA every three weeks as determined based on the results of the Phase Ib part. The primary endpoint of the Phase II part was objective response rate at 24 weeks after treatment began, with select secondary endpoints including objective response rate, disease control rate, progression-free survival, and duration of response. Currently, the Phase II part is underway, with enrollment expanded for the endometrial cancer cohort.

About Renal Cell Carcinoma

In 2012, the number of patients with renal cancer was estimated to be approximately 338,000 worldwide, including approximately 58,000 in the United States, 115,000 in Europe and 17,000 in Japan.² In the United States, approximately 63,990 new cases were estimated to occur in 2017.³ Approximately 25–30 percent of patients are estimated to present with metastatic disease at time of diagnosis.⁴ Renal cell carcinoma comprises more than approximately 90 percent of all malignancies of the kidney,⁵ and originates from malignant cells in the lining of the tubules of the kidney.³ The average age of a renal cancer diagnosis is 64, and it is more likely to affect men than women.⁶ For advanced and/or metastatic renal cell carcinoma that is difficult to treat with surgery, the standard treatment is molecular targeted drug therapy.⁷ However, this remains a disease with significant unmet medical need.³

About LENVIMA® (lenvatinib mesylate)

Discovered and developed in-house by Eisai, LENVIMA is an orally administered multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFR α ; KIT; and RET) involved in tumor proliferation.

Currently, Eisai has obtained approval for LENVIMA as a treatment for refractory thyroid cancer in over 50 countries, including the United States, Japan, and in Europe. Additionally, Eisai has obtained approval for the agent in combination with everolimus as a treatment for renal cell carcinoma (second-line) in over 40 countries, including the United States and in Europe. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma.

Furthermore, in a Phase III clinical study (Study 304) comparing safety and efficacy of the agent versus sorafenib for the treatment of hepatocellular carcinoma, LENVIMA achieved its primary endpoint of overall survival, meeting the statistical criteria for non-inferiority to sorafenib. Eisai has submitted applications for an indication covering hepatocellular carcinoma in Japan (June 2017), the United States and Europe (July 2017), China (October 2017) as well as Taiwan (December 2017).

Additionally, a Phase III clinical study (Study 307) of LENVIMA in combination with either everolimus or KEYTRUDA as a first line treatment for renal cell carcinoma is underway.



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.

MSD has the industry's largest immuno-oncology clinical research program, which currently involves more than 650 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 Eisai Co., Ltd.

Eisai Co., Ltd. is a leading global research and development-based pharmaceutical company headquartered in Japan. 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. With approximately 10,000 employees working across our global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realize our *hhc* philosophy by delivering innovative products in various therapeutic areas with high unmet medical needs, including Oncology and Neurology.

As a global pharmaceutical company, our mission extends to patients around the world through our investment and participation in partnership-based initiatives to improve access to medicines in developing and emerging countries.

For more information about Eisai Co., Ltd., please visit www.eisai.com.

About MSD

For more than a century, MSD, a leading global biopharmaceutical company, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. MSD is a trade name of Merck & Co., Inc., with headquarters in Kenilworth, N.J., USA. 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, MSD 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.msd.com.

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¹ Lee CH, et al. A Phase 1b/2 Trial of Lenvatinib + Pembrolizumab in Patients With Renal Cell Carcinoma. *ESMO Congress Abstract*, 2017; #8470

² GLOBOCAN2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. <http://globocan.iarc.fr/>

³ "Cancer Stat Facts: Kidney and Renal Pelvis Cancer." Surveillance, Epidemiology, and End Results Program (SEER), National Cancer Institute, <https://seer.cancer.gov/statfacts/html/kidrp.html>.

⁴ Gupta, Kiran. "Epidemiologic and Socioeconomic Burden of Metastatic Renal Cell Carcinoma (MRCC): A Literature Review." *Cancer Treatment Reviews*, vol. 34, no. 3, May 2008, [http://www.cancertreatmentreviews.com/article/S0305-7372\(07\)00187-9/fulltext](http://www.cancertreatmentreviews.com/article/S0305-7372(07)00187-9/fulltext).

⁵ Eble J.N, et al. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs, World Health Organisation classification of tumours. (International Agency for Research on Cancer, Lyon, France in 2004)

⁶ "What Are the Key Statistics About Kidney Cancer?" About Kidney Cancer, American Cancer Society, Aug. 2017, <https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html>.

⁷ Stukalin, Igor. "Contemporary Treatment of Metastatic Renal Cell Carcinoma." *Oncology Reviews*, vol. 10, no. 1, 2016, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4943094/#>.

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