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New Data on LENVIMA® (lenvatinib) Plus KEYTRUDA® (pembrolizumab) Versus Sunitinib in First-Line Treatment for Patients With Advanced Renal Cell Carcinoma From Pivotal Phase 3 CLEAR/KEYNOTE-581 Trial Presented at 2021 ASCO Annual Meeting

Results From New Analysis Evaluating Health-Related Quality of Life (HRQoL) Based on Patient-Reported Outcomes Using Three HRQoL Scales

TOKYO and KENILWORTH, N.J., June 7, 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 new investigational data from the pivotal Phase 3 CLEAR(Study 307)/KEYNOTE-581 trial, which evaluated the combinations 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., and LENVIMA plus everolimus versus sunitinib for the first-line treatment of patients with advanced renal cell carcinoma (RCC). Results from a new analysis evaluating health-related quality of life (HRQoL) based on patient-reported outcomes are being presented during an oral abstract session at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract #4502). Data from CLEAR/KEYNOTE-581 were originally presented at the 2021 Genitourinary Cancers Symposium (ASCO GU) and published in the *New England Journal of Medicine*, and data from this trial are currently under review with the U.S. Food and Drug Administration (FDA).

“This new analysis expands our understanding of the results we’ve seen from the CLEAR/KEYNOTE-581 trial in the treatment of patients with advanced renal cell carcinoma,” said Dr. Robert Motzer, Medical Oncologist, Kidney Cancer Section Head, Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center. “The additional data showed an improvement of specific health-related quality of life measures for patients who received LENVIMA plus KEYTRUDA compared with sunitinib, supporting the importance of this combination as a potential new first-line treatment option for patients.”

“We continue to see an increasing number of patients diagnosed with advanced renal cell carcinoma and remain committed to improving outcomes for those facing this difficult-to-treat disease,” said Dr. Gregory Lubiniecki, Vice President, Oncology Clinical Research, Merck & Co., Inc., Kenilworth, N.J., U.S.A. Research Laboratories. “This new analysis builds on earlier findings from the CLEAR/KEYNOTE-581 trial and further supports the potential use of KEYTRUDA plus LENVIMA for the treatment of patients in the first-line setting.”

“This analysis addresses questions of interest to healthcare professionals who treat patients with advanced renal cell carcinoma and reinforces the LENVIMA plus KEYTRUDA combination as a possible new treatment option for patients with this disease,” said Dr. Takashi Owa, Chief Medicine Creation Officer and Chief Discovery Officer, Oncology Business Group at Eisai. “These results reflect Eisai and Merck’s shared commitment to relentlessly pursue thorough scientific investigations with the goal of improving cancer care.”

Data From Health-Related Quality-of-Life (HRQoL) Analysis From CLEAR/KEYNOTE-581

In an analysis of a secondary endpoint of HRQoL scores in the CLEAR/KEYNOTE-581 trial, LENVIMA plus KEYTRUDA and LENVIMA plus everolimus were evaluated to determine the impact on HRQoL compared to sunitinib in patients with advanced RCC. This was assessed based on patient-reported outcomes using three HRQoL and symptom measures: Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms (FKSI-DRS), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer – Core 30 (EORTC QLQ-C30) and European Quality of Life Five-Dimensions – 3-Level System (EuroQoL EQ-5D-3L). Unless otherwise noted, HRQoL analyses were based on data from randomized patients who received at least one dose of study treatment. No adjustments for multiple testing or estimation were used; *p*-values (two-sided) and confidence intervals (CI) are nominal and descriptive. Longitudinal change from baseline was assessed by mixed model analysis. Least squares mean differences (LSMD) and 95% CI were calculated from baseline. Time to deterioration (based on changes in HRQoL and disease-related symptom scores \geq meaningful thresholds) was assessed using time to first deterioration (TTD), which is the number of weeks between randomization and the first deterioration event, and time until definitive deterioration (TUDD), which is the number of weeks between randomization and the earliest deterioration event with no subsequent recovery above the deterioration threshold or no subsequent HRQoL assessment data. All times to deterioration were calculated and compared using the Kaplan-Meier method, stratified log-rank tests and Cox models.

LENVIMA plus KEYTRUDA demonstrated similar changes from baseline at mean follow-up (Week 46) on 14 out of 18 HRQoL and disease-related symptom scores and better HRQoL and disease-related symptom scores for the following measures (LSMD [95% CI]): physical functioning (3.01 [0.48, 5.54]), fatigue (-2.80 [-5.52, -0.08]), dyspnea (-2.79 [-5.33, -0.25]) and constipation (-2.19 [-4.19, -0.18]), as measured by the QLQ-C30, versus sunitinib. LENVIMA plus everolimus demonstrated similar changes from baseline at mean follow-up (Week 46) on 14 out of 18 HRQoL and disease-related symptom scores and worse HRQoL and disease-related symptom scores in the following measures (LSMD [95% CI]): Global Health Score/QoL (-2.81 [-5.08, -0.54]), pain (2.80 [0.11, 5.49]), appetite loss (4.23 [1.34, 7.13]) and diarrhea (5.26 [2.61, 7.91]) compared to sunitinib.

LENVIMA plus KEYTRUDA demonstrated a similar TTD in 14 out of 18 HRQoL and disease-related symptom scores, and a delay in TTD for physical functioning, dyspnea, appetite loss, and EQ-5D visual analog scale compared to sunitinib. LENVIMA plus KEYTRUDA demonstrated a delay in TUDD in 16 out of 18 HRQoL and disease-related symptom scores and a similar TUDD for cognitive functioning and financial difficulties compared to sunitinib.

Dr. Motzer has provided consulting and advisory services for Merck and Eisai.

About LENVIMA® (lenvatinib) Capsules

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 (PDGFR α), 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. The combination of lenvatinib and everolimus showed increased anti-angiogenic and anti-tumor activity as demonstrated by decreases in human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and decreases in tumor volume in mouse xenograft models of human renal cell cancer greater than those with either drug 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 70 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 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 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.

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 CLEAR(Study 307)/KEYNOTE-581

The CLEAR/KEYNOTE-581 trial is a multicenter, randomized, open-label, Phase 3 trial (ClinicalTrials.gov, [NCT02811861](https://clinicaltrials.gov/ct2/show/study/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 progression-free survival, as assessed by independent review per RECIST v1.1. Secondary endpoints include overall survival, objective response rate, HRQoL and safety. A total of 1,069 patients were randomized (1:1:1) to receive LENVIMA (20 mg orally once daily) in combination with KEYTRUDA (200 mg intravenously [IV] every three weeks for up to 24

months); 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). Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by independent radiologic review committee (IRC) using RECIST v1.1. Administration of LENVIMA plus KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA 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 eight weeks.

About Renal Cell Carcinoma (RCC)^{1,2,3,4,5,6}

Worldwide, it is estimated there were more than 431,000 new cases of kidney cancer diagnosed and more than 179,000 deaths from the disease in 2020. In Japan, there were more than 25,000 new cases and 8,000 deaths in 2020. In the U.S., it is estimated there will be nearly 76,000 new cases of kidney cancer diagnosed and almost 14,000 deaths from the disease in 2021. Renal cell carcinoma is by far the most common type of kidney cancer; about nine out of 10 kidney cancer diagnoses are RCC. Renal cell carcinoma is about twice as common in men as in women. 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. Survival is highly dependent on the stage at diagnosis, and the five-year survival rate is 13% for patients with metastatic disease.

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 (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.).

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.

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 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).

¹ International Agency for Research on Cancer, World Health Organization. "Kidney Fact Sheet." Cancer Today, 2020. <https://gco.iarc.fr/today/data/factsheets/cancers/29-Kidney-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 American Cancer Society. Key Statistics About Kidney Cancer. <https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html>.

⁴ Thomas A. Z. et al. The Role Of Metastasectomy In Patients With Renal Cell Carcinoma With Sarcomatoid Dedifferentiation: A Matched Controlled Analysis. *The Journal of Urology*. 2016 Sep; 196(3): 678–684. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5014677/pdf/nihms773463.pdf> .

⁵ Shinder B. et al. Surgical Management of Advanced and Metastatic Renal Cell Carcinoma: A Multidisciplinary Approach. *Frontiers in Oncology*. 2017; 7: 107. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5449498/#_ffn_sectitle .

⁶ Padala, S. A., Barsouk, A., Thandra, K. C., Saginala, K., Mohammed, A., Vakiti, A., Rawla, P., & Barsouk, A. (2020). Epidemiology of Renal Cell Carcinoma. *World journal of oncology*, 11(3), 79–87. <https://doi.org/10.14740/wjon1279> .

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