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Eisai and Merck Receive Complete Response Letter for LENVIMA® (lenvatinib) plus KEYTRUDA® (pembrolizumab) Combination as First-Line Treatment for Unresectable Hepatocellular Carcinoma

TOKYO and KENILWORTH, N.J. [July 8, 2020] – 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) announced today that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) regarding Eisai's and Merck's applications seeking accelerated approval of LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, plus KEYTRUDA, Merck's anti-PD-1 therapy, for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).

The applications were based on data from the Phase 1b Study 116/KEYNOTE-524 trial, which showed clinically meaningful efficacy in the single-arm setting. These data were recently presented at the 2020 American Society of Clinical Oncology Annual Meeting and supported a Breakthrough Therapy designation granted by the FDA in July 2019. Ahead of the PDUFA action dates of Eisai's and Merck's applications, another combination therapy was approved based on a randomized controlled trial that demonstrated overall survival. Consequently, the CRL stated that the applications do not provide evidence that KEYTRUDA in combination with LENVIMA represents a meaningful advantage over available therapies for the treatment of unresectable or metastatic HCC with no prior systemic therapy for advanced disease. Since the applications for Study 116/KEYNOTE-524 no longer meet the criteria for accelerated approval, both companies plan to work with the FDA to take appropriate next steps, which include conducting a well-controlled clinical trial that demonstrates substantial evidence of effectiveness and the clinical benefit of the combination. As such, LEAP-002, the Phase 3 trial evaluating the LENVIMA plus KEYTRUDA combination as a first-line treatment for advanced HCC, is currently underway and fully enrolled. The CRL does not impact the current approved indications for LENVIMA or for KEYTRUDA.

Eisai and Merck are continuing to evaluate the LENVIMA plus KEYTRUDA combination across 13 different tumor types in 18 clinical trials including the LEAP (LEnvatinib And Pembrolizumab) clinical program.

About Study 116/KEYNOTE-524

Study 116/KEYNOTE-524 (ClinicalTrials.gov, NCT03006926) is a Phase 1b, open-label, single-arm trial evaluating the LENVIMA plus KEYTRUDA combination in 100 patients with unresectable HCC with no prior systemic therapy. Patients were treated with LENVIMA 8 or 12 mg (based on baseline body weight <60 kilograms or ≥60 kilograms, respectively) orally once daily in combination with KEYTRUDA 200 mg intravenously every three weeks. The primary endpoints are objective response rate (ORR) and duration of response (DOR) by modified Response Evaluation Criteria in Solid Tumors (mRECIST) and RECIST v1.1 per independent imaging review (IIR). Secondary endpoints include progression-free survival (PFS), time to progression (TTP) and overall survival (OS). At data cutoff (October 31, 2019) and a median duration of follow-up of 10.6 months (95% CI: 9.2-11.5), 37 patients were still on study treatment (LENVIMA plus KEYTRUDA: n=34; LENVIMA only: n=3), and median duration of treatment exposure to the LENVIMA plus KEYTRUDA combination was 7.9 months (range: 0.2-31.1).

The final analysis of the study's primary endpoints showed the LENVIMA plus KEYTRUDA combination demonstrated an ORR of 36% (n=36) (95% CI: 26.6-46.2), with a complete response rate of 1% (n=1) and a partial response rate of 35% (n=35), and a median DOR of 12.6 months (95% CI: 6.9-not estimable [NE]), using RECIST v1.1 criteria per IIR. As assessed using mRECIST criteria per IIR, the LENVIMA plus KEYTRUDA combination demonstrated an ORR of 46% (n=46) (95% CI: 36.0-56.3), with a complete response rate of 11% (n=11) and a partial response rate of 35% (n=35), and a median DOR of 8.6 months (95% CI: 6.9-NE).

Treatment-related adverse events (TRAEs) led to discontinuation of LENVIMA and KEYTRUDA in 6% of patients, of LENVIMA in 14% of patients, and of KEYTRUDA in 10% of patients. Grade ≥3 TRAEs occurred in 67% of patients (Grade 3: 63%; Grade 4: 1%; Grade 5: 3%). There was one Grade 4 TRAE (leukopenia/neutropenia), and there were three treatment-related deaths (acute respiratory failure/acute respiratory distress syndrome, intestinal perforation and abnormal hepatic function; n=1 for each). The most common TRAEs of any grade (≥20%) were hypertension (36%), diarrhea (35%), fatigue (30%), decreased appetite (28%), hypothyroidism (25%), palmar-plantar erythrodysesthesia syndrome (23%), decreased weight (22%), dysphonia (21%), increased aspartate aminotransferase (20%) and proteinuria (20%).

About LENVIMA

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 (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 60 countries including Japan, the United States, in Europe and Asia, and for unresectable hepatocellular carcinoma in over 55 countries including Japan, the United States, in Europe, China and in Asia. Additionally, it is also approved in combination with everolimus as a treatment for renal cell carcinoma following prior antiangiogenic therapy in over 55 countries, including the United

States, in Europe and Asia. 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 countries including the United States, Australia, and Canada. Continued approval for this indication is contingent upon verification and description of clinical benefit in the confirmatory trials. In Europe, the agent was launched under the brand name Kisplyx® for renal cell carcinoma.

About KEYTRUDA

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 1,200 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.

Eisai's Focus on Cancer

Eisai focuses on the development of anticancer drugs, targeting the tumor microenvironment (with experience and knowledge from Halaven and Lenvima) 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 become a frontrunner in oncology. Eisai will 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 more than 125 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., U.S.A.

This news release of Merck & Co., Inc., Kenilworth, N.J., U.S.A. (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 recent 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 2019 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).

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