

FOR IMMEDIATE RELEASE

**EISAI AND MERCK & CO., INC., KENILWORTH, N.J., U.S.A. ANNOUNCE DATA
AT 2018 ASCO ANNUAL MEETING FROM INVESTIGATIONAL STUDIES OF
LENVIMA® AND KEYTRUDA® COMBINATION THERAPY
IN FOUR DIFFERENT TUMOR TYPES**

- **First presentation of LENVIMA/KEYTRUDA data in patients with unresectable hepatocellular carcinoma (HCC), which aims to be the first systemic combination of a TKI and immunotherapy for these patients, as well as squamous cell carcinoma of the head and neck (SCCHN)**
- **Updated results show antitumor activity with a consistent safety profile in advanced renal cell carcinoma (RCC) and advanced endometrial carcinoma (EC)**
- **The LENVIMA/KEYTRUDA combination was recently granted U.S. Food and Drug Administration (FDA) Breakthrough Therapy Designation for advanced RCC**
- **Phase III trials underway in advanced RCC (NCT02811861) and advanced EC (NCT03517449)**

TOKYO Jun 4, 2018 – 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 results from presentations of new data and analyses of LENVIMA® (lenvatinib), an orally available kinase inhibitor discovered by Eisai, in combination with Merck & Co., Inc., Kenilworth, N.J., U.S.A.’s anti-PD-1 therapy, KEYTRUDA® (pembrolizumab), in four different tumor types: unresectable hepatocellular carcinoma (HCC) (Abstract #4076), squamous cell carcinoma of the head and neck (SCCHN) (Abstract #6016), advanced renal cell carcinoma (RCC) (Abstract #4560), and advanced endometrial carcinoma (EC) (Abstract #5596 and Abstract #5597). The data are included in presentations at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago from June 1-5. LENVIMA and KEYTRUDA are not approved for use in combination in any cancer types today.

“The data we have observed in the combination studies of LENVIMA plus KEYTRUDA have fueled our commitment to help meet the diverse health care needs of patients living with cancer through clinical studies and research in specific tumor types that are notoriously difficult to treat and continue to have a significant need for new therapeutic options,” said Alton Kremer, MD, PhD, Chief Clinical Officer and Chief Medical Officer, Oncology Business Group at Eisai. “We are pleased to share the activity observed in clinical studies of the LENVIMA plus KEYTRUDA combination, as well as rationale for the combination in advanced endometrial carcinoma through translational research.”

“With these data at ASCO, we are continuing to see encouraging overall response rates, as well as a safety profile that supports the scientific rationale of adding LENVIMA to KEYTRUDA,” said Dr. Roy Baynes, Senior Vice President and Head of Global Clinical Development, Chief Medical Officer, Merck & Co., Inc., Kenilworth, N.J., U.S.A. “These findings add to the growing body of evidence showing the potential of this combination regimen across a number of tumor types and underscore the strategy behind our collaboration with Eisai.”

This release discusses investigational uses for FDA-approved products. It is not intended to convey conclusions about efficacy and safety. There is no guarantee that any investigational uses of FDA-approved products will successfully complete clinical development or gain FDA approval.

1. Early phase results from Study 116/KEYNOTE-524 support further investigation in unresectable HCC

Study 116/KEYNOTE-524 is a Phase Ib open-label, single-arm multicenter study evaluating the tolerability and safety of the combination of LENVIMA (12 mg/day for patients weighing \geq 60 kg, 8 mg/day for patients weighing < 60 kg) and KEYTRUDA (200 mg intravenously every 3 weeks) in patients with unresectable HCC, Barcelona Clinic Liver Cancer (BCLC) stage B (not eligible for transarterial chemoembolization [TACE]) or C, Child-Pugh class A, and ECOG performance status of 0 or 1. The primary endpoint was safety; secondary and exploratory endpoints included overall survival (OS), objective response rate (ORR), progression-free survival (PFS) and time to progression (TTP) using modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Tumor assessments of complete or partial response (CR or PR) were confirmed greater than or equal to four weeks after initial response. Part 1 evaluated tolerability by assessing dose-limiting toxicities (DLTs) during the first cycle of treatment in patients for whom no other appropriate therapy was available. After tolerability was confirmed, additional patients with no prior systemic therapy for unresectable HCC were enrolled (Part 2). The expansion part of the study will evaluate objective response rate and duration of response as measured by mRECIST.

Data presented at ASCO are from one abstract:

A Phase Ib trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC) (Abstract #4076)

As of March 22, 2018, 30 patients were enrolled in this trial (Part 1, n=6; Part 2, n=24). No dose-limiting toxicities were reported. Four patients discontinued due to treatment emergent adverse events (TEAEs). The most common TEAEs (any grade) were decreased appetite (53.3%) and hypertension (53.3%), diarrhea (43.3%) and fatigue (40.0%). Tumor assessments were performed according to mRECIST by the investigators. At data cutoff, the ORR (including cases of unconfirmed CR and PR) was 42.3% (95% CI: 23.4-63.1). A second scan was performed at least four weeks following the initial response, which demonstrated a confirmed ORR of 26.9% (95% CI: 11.6-47.8). Median duration of PFS was 9.7 months (95% CI: 5.55-NE). None of the treated patients experienced progressive disease (PD) as best overall response (BOR). Twenty-three patients (Part 1, n=3, Part 2, n=20) are still undergoing study treatment. Based on the safety and efficacy data seen thus far, the protocol has been amended to enroll approximately 94 patients to the Part 2 expansion cohort.

2. New and updated results from Study 111/KEYNOTE-146 support further evaluation in SCCHN, RCC, and EC as well as biomarker analysis with clinical serum samples from patients with advanced EC to clarify combination rationale

Study 111/KEYNOTE-146 is a multicenter, open-label, single-arm Phase Ib/II basket trial evaluating the combination of LENVIMA (20 mg/day) with KEYTRUDA (200 mg intravenously every three weeks) in patients with selected solid tumors. Patients were not preselected based on PD-L1 status. The primary endpoint of the Phase Ib study was to determine the maximum tolerated dose of KEYTRUDA and LENVIMA in combination. The primary endpoint of the Phase II portion is investigator-assessed ORR at

week 24 based on immune-related RECIST (irRECIST). The secondary efficacy endpoints included ORR, PFS, and duration of response for patients with complete or partial responses.

Data presented at ASCO are from four abstracts:

1) *A Phase Ib/II trial of lenvatinib plus pembrolizumab in patients with squamous cell carcinoma of the head and neck (Abstract #6016)*

As of December 1, 2017, 22 patients with measurable, confirmed metastatic SCCHN and ECOG performance status of 0 or 1 were enrolled in this cohort. 90.9% of patients received at least one prior anticancer therapy. At data cutoff, ORR at week 24 was 36.4% (95% CI: 17.2-59.3), overall ORR was 40.9% (including 1 CR and 8 PRs; 95% CI: 20.7-63.6), and PFS rate at 12 months was 41.9% (95% CI: 17.6-64.7). None of the treated patients experienced progressive disease (PD) as best overall response (BOR), and tumor size reduction was observed in the majority of the patients. Grade 3 or 4 TRAEs occurred in 72.7% of patients (Grade 4 TRAEs in 4.5%). The most common TRAEs (any grade) were fatigue (50.0%), hypertension (40.9%), diarrhea (36.4%), decreased appetite (31.8%), oropharyngeal pain (31.8%) and stomatitis (31.8%). Overall, the study demonstrated promising clinical activity, supporting further evaluation of the combination in patients with SCCHN.

2) *Lenvatinib + pembrolizumab in patients with renal cell carcinoma: updated results (Abstract #4560)*

This cohort enrolled 30 patients with metastatic clear cell RCC and measurable disease per irRECIST. In addition to the assessments performed by investigators per irRECIST, these updated data include tumor assessments performed retrospectively by independent radiographic review (IRR) per irRECIST and RECIST 1.1, as well as the first report of PFS results in this cohort. ORR at week 24 was 63.3% (95% CI: 43.9–80.1), based on investigator assessment per irRECIST. At data cutoff on December 1, 2017, overall ORR was 70.0% (95% CI: 50.6-85.3) based on investigator assessment per irRECIST; median duration of response was 18.4 months (95% CI: 10.3-NE), and median PFS was not estimable (95% CI: 11.6-NE). Based on the IRR per irRECIST, ORR was 66.7% (95% CI: 47.2-82.7), median duration of response was not estimable (95% CI: 14.9-NE), and median PFS was 18.0 months (95% CI: 10.2-NE); per RECIST 1.1, ORR was also 66.7% (95% CI: 47.2-82.7), median duration of response was 16.6 months (95% CI: 8.9-NE), and median PFS was 18.0 months (95% CI: 9.6-NE). Grade 3 or 4 AEs occurred in 22 patients (73.3%), and eight patients (26.7%) discontinued treatment due to an AE. The most common AEs (any grade) were diarrhea (83.3%), fatigue (73.3%), hypothyroidism (70.0%), stomatitis (63.3%) and nausea (60.0%). A Phase III trial comparing the LENVIMA plus KEYTRUDA combination and the LENVIMA plus everolimus combination versus sunitinib monotherapy for the first-line treatment of advanced RCC is currently recruiting (CLEAR; NCT02811861; please visit clinicaltrials.gov for more information).

3) *Lenvatinib + pembrolizumab in patients with advanced endometrial cancer: Updated results (Abstract #5596)*

As of data cut-off of December 15, 2017, efficacy and safety analyses are summarized in the poster for 53 patients with histologically confirmed metastatic EC, irrespective of microsatellite instability (MSI) or mismatch repair (MMR) status, and measurable disease per irRECIST. Four (7.5%) patients were MSI-high, 45 (85%) were non MSI-H (MSS), and four (7.5%) patients' MSI status was not known. At data cutoff, ORR at week 24 based on investigator assessment was 39.6% (95% CI: 26.5-54.0); overall ORR was the same. Objective responses were seen regardless of tumor MSI status. Confirmed objective responses were seen in patients with MSS tumors (16/45 [ORR 35.6%]; 95% CI: 21.9-51.2) and MSI-H tumors (2/4 [ORR 50.0%]; 95% CI: 6.8-93.2). Secondary analysis of tumor efficacy by independent radiology review (IRR) showed an ORR at

week 24 of 45.3% (95% CI: 31.6-59.6) and an overall ORR of 47.2% (95% CI: 33.3-61.4) with 22 partial responses and three complete responses. Of responding patients, 83.0% (95% CI: 55.9-94.2) had a response duration of six months or more and 64.5% (95% CI: 32.8-84.2) had a response duration of 12 months or more per investigator assessment, and median duration of response had not yet been reached (95% CI: 7.4-NE). When assessed by IRR, among responding patients, 79.3% (95% CI: 48.5-92.9) had a response duration of 12 months or more, and median duration of response was also not yet reached (95% CI: 5.8-NE). Median PFS was 7.4 months (95% CI: 5.0-not estimable [NE]) per investigator assessment. Most patients showed a decrease in the mean maximum percentage change from baseline in the sum of the diameters of target lesions, regardless of MSI or PD-L1 expression status. Grade 3 treatment-related adverse events (TRAEs) occurred in 37 patients (70%); there were no Grade 4 TRAEs. Five patients (9%) discontinued treatment due to TRAEs. The most common TRAEs (any grade) were hypertension (59%), fatigue (55%), diarrhea (51%), hypothyroidism (47%), decreased appetite (40%), nausea (38%) and stomatitis (34%). A randomized, international, 2-arm, Phase III study in recurrent endometrial carcinoma is underway (Study 309/KEYNOTE-775; NCT03517449; please visit clinicaltrials.gov for more information).

4) *Biomarker results and preclinical rationale for combination of lenvatinib and pembrolizumab in advanced endometrial carcinoma (Abstract #5597)*

In an exploratory analysis, 41 candidate serum biomarkers were assessed in immunoassay panels of serum samples collected at baseline, on cycle one, day 15 (C1D15); and cycle two, day one (C2D1) from 37 patients with EC receiving the LENVIMA plus KEYTRUDA combination. In patients with advanced EC, treatment with the combination was associated with changes in several serum biomarkers, including interferon (IFN)- γ and IFN- γ -regulated chemokines, some of which may be associated with tumor response. In addition to the exploratory analysis from Study 111/KEYNOTE-146, preclinical studies on the immunomodulatory and antitumor activity of LENVIMA when combined with PD-1/PD-L1 blockade were presented to more clearly define the basis of combination LENVIMA plus KEYTRUDA. The *in vivo* preclinical models suggest that LENVIMA monotherapy may decrease the population of tumor-associated macrophage in the tumor microenvironment and the combination therapy may act via a mechanism that includes the interferon signaling pathways to enhance antitumor activity over each monotherapy. Overall, these findings provide rationale for the antitumor activity of LENVIMA plus KEYTRUDA in combination.

About LENVIMA (lenvatinib mesylate)

Discovered 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 pathway-related RTKs (including the platelet-derived growth factor (PDGF) receptor PDGFR α ; KIT; and RET) involved in tumor angiogenesis, tumor progression and modification of tumor immunity.

Currently, LENVIMA is approved as a treatment for refractory thyroid cancer in over 50 countries, including the United States, Japan, in Europe and Asia. 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.

Outside of Japan, Eisai has submitted applications for an indication covering hepatocellular carcinoma in the United States and Europe (July 2017), China (October 2017), Taiwan (December 2017) and other countries.

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. has the industry's largest immuno-oncology clinical research program, which currently involves more than 750 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 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. entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA. Under the agreement, the companies will develop and commercialize LENVIMA jointly, both as monotherapy and in combination with Merck & Co., Inc. Kenilworth N.J., U.S.A.'s anti-PD-1 therapy KEYTRUDA® (pembrolizumab). In addition to ongoing clinical studies of the combination, the companies will jointly initiate new clinical studies evaluating the LENVIMA/KEYTRUDA combination to support 11 potential indications in six types of cancer (endometrial cancer, non-small cell lung cancer, hepatocellular carcinoma, head and neck cancer, bladder cancer and melanoma), as well as a basket trial targeting multiple cancer types.

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