Further Study of Combination of Eisai’s Lenvatinib and Merck’s Pembrolizumab in Previously Treated Patients with Metastatic Endometrial Cancer Supported by Interim Analysis of Ongoing Phase 1b/2 Trial

- Interim results of first evaluable cohort (metastatic endometrial cancer) of Study 111, the Phase 1b/2 trial evaluating lenvatinib in combination with pembrolizumab in selected solid tumors, to be presented at 2017 ASCO Annual Meeting

WOODCLIFF LAKE, N.J., June 3, 2017–Eisai Inc. today announced interim results from the first evaluable cohort of Study 111, a Phase 1b/2 study investigating lenvatinib (marketed as Lenvima®), a multiple receptor tyrosine kinase inhibitor, in combination with Merck’s (known as MSD outside the United States and Canada) pembrolizumab (marketed as KEYTRUDA®), an anti-PD-1 therapy, in patients with selected solid tumors. In this cohort of previously treated patients (median = 2 prior therapies) with metastatic endometrial cancer (n=23), the confirmed objective response rate (ORR) at week 24, the primary endpoint of the study, was 47.8% (95% CI: 26.8 – 69.4) based on investigator assessment and 52.2% based on independent radiologic review (IRR) (95% CI: 30.6 – 73.2), all of which were partial responses. No new safety signals were found and toxicities were managed with dose interruption, modification or discontinuation. Lenvima and KEYTRUDA are not approved for use in combination, and neither drug is approved for the treatment of endometrial cancer. These results will be presented today at the 2017 Annual Meeting of the American Society of Clinical Oncology (ASCO) in Chicago during the Gynecologic Cancer Poster Session from 1:15-4:45 p.m. CT (Abstract No. 5598).

Metastatic endometrial cancer is a difficult-to-treat form of the disease as response rates for patients who have received first-line treatment are often low. Beyond chemotherapy and hormone therapy, there are no FDA-approved therapies for these patients.

“We are encouraged by the results of this study in which nearly half of the patients who have received prior systemic therapy for the treatment of recurrent advanced or metastatic endometrial cancer responded to this combination therapy,” said Vicky Makker, MD, gynecologic medical oncologist, Memorial Sloan Kettering Cancer Center and lead investigator. “Women whose endometrial cancer has recurred are in need of additional therapeutic options, and we look forward to learning more regarding the potential of this combination regimen for these women.”

Secondary endpoints include progression-free survival (PFS), disease control rate (DCR; partial response and stable disease), clinical benefit rate (CBR; partial response and durable stable disease), duration of response (DOR) and safety and tolerability. Median PFS was 9.7 months (95% CI: 4.2 – NE) based on investigator assessment and was not reached by IRR. DCR was 95.7% (95% CI: 78.1 – 99.9) based on investigator assessment and 91.3% (95% CI: 72.0 – 98.9) based on IRR. CBR was 73.9% (95% CI: 51.6 – 89.8) based on investigator assessment and 65.2% (95% CI: 42.7 – 83.6) based on IRR. Median DOR was not reached at the time of analysis (2.6 – NE). Tumor shrinkage was observed regardless of MSI (microsatellite instability) status. All patients had a treatment-emergent adverse event (TEAE) and a treatment-related TEAE. The most common TEAEs for the combination regimen were hypertension, fatigue, diarrhea, nausea, and arthralgia. Ten patients experienced serious TEAEs; the only serious TEAE experienced by more than one patient was hypertension.

“Given the response rates demonstrated in this study, we are enthusiastic about continuing further research of this immuno-targeted therapy combination regimen in women previously treated for...
metastatic endometrial cancer,” said Alton Kremer, MD, PhD, Chief Clinical Officer and Chief Medical Officer, Oncology Business Group at Eisai.

"Little progress has been made in bringing forward new approaches for metastatic endometrial cancer. The interim results of the combination of these two mechanisms are encouraging and further support the potential for pembrolizumab and lenvatinib to help women with this aggressive and difficult-to-treat cancer," said Dr. Eric Rubin, vice president and therapeutic area head, oncology early stage development, Merck Research Laboratories.

Lenvima (lenvatinib) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Lenvima is also indicated in combination with everolimus for the treatment of patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy. This release discusses an investigational use for FDA-approved products. Lenvima is not approved for use in combination with KEYTRUDA. This release is not intended to convey any conclusions about efficacy or safety of lenvatinib, pembrolizumab or any combination of these two agents. There is no guarantee that any investigational uses of such FDA-approved products will successfully complete clinical development or gain FDA approval.

KEYTRUDA® is a registered trademark of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Kenilworth, NJ, USA.

About Study 111
Study 111 is a multicenter, open-label, single-arm Phase 1b/2 basket trial of the combination of lenvatinib (20 mg/day) with pembrolizumab (200 mg intravenously every 3 weeks) in patients with selected solid tumors. The primary endpoint of the Phase 1b study was to determine the maximum tolerated dose of pembrolizumab and lenvatinib in combination. The primary endpoint of the Phase 2 study is investigator-assessed ORR based on immune-related RECIST at week 24. The secondary endpoints include progression-free survival, duration of response, disease control rate, and clinical benefit rate. Twenty three patients with previously treated metastatic endometrial cancer were evaluated in the endometrial cohort. The study is being conducted under an existing clinical trial collaboration agreement between the two companies.

About Endometrial Cancer
Endometrial cancer occurs in the tissues of the endometrium, which is the inner layer or inner lining of the uterus. In the United States, endometrial cancer is the most common cancer of the female reproductive system. This year approximately 61,300 new cases of endometrial cancer will occur, and an estimated 10,900 women will die from this disease. Nine percent of women have metastatic disease at diagnosis and the 5-year relative survival rate for these women is just over 16%.

About Lenvima® (lenvatinib)
Lenvima® (lenvatinib) is a kinase inhibitor that is indicated for:

- Differentiated Thyroid Cancer (DTC): single agent for patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC.
- Renal Cell Cancer (RCC): in combination with everolimus for patients with advanced RCC following one prior anti-angiogenic therapy.

Lenvatinib, discovered and developed by Eisai, is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1-3. Lenvatinib also inhibits other RTKs 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. The combination of lenvatinib and everolimus showed increased anti-angiogenic and anti-tumor activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and tumor volume in mouse xenograft models of human renal cell cancer greater than each drug alone.
Selected Safety Information

Warnings and Precautions

- In DTC, hypertension was reported in 73% of patients on LENVIMA vs 16% with placebo (44% vs 4% grade ≥3). In RCC, hypertension was reported in 42% of patients on LENVIMA + everolimus vs 10% with everolimus alone (13% vs 2% grade ≥3). Systolic blood pressure ≥160 mmHg occurred in 29% of patients, and 21% of patients had a diastolic blood pressure ≥100 mmHg in the LENVIMA + everolimus–treated group. Blood pressure should be controlled prior to treatment and monitored throughout. Withhold dose for grade 3 hypertension despite optimal antihypertensive therapy; resume at reduced dose when controlled at grade ≤2. Discontinue for life-threatening hypertension

- In DTC, cardiac dysfunction was reported in 7% of patients on LENVIMA vs 2% with placebo (2% vs 0% grade ≥3). In RCC, decreased ejection fraction and cardiac failure were reported in 10% of patients on LENVIMA + everolimus vs 6% with everolimus alone (3% vs 2% grade 3). Monitor for signs/symptoms of cardiac decompensation. Withhold LENVIMA for development of grade 3 cardiac dysfunction until improvement to grade 0, 1, or baseline. Resume at reduced dose or discontinue based on severity and persistence of cardiac dysfunction. Discontinue for grade 4 cardiac dysfunction

- In DTC, arterial thromboembolic events were reported in 5% of patients on LENVIMA vs 2% with placebo (3% vs 1% grade ≥3). In RCC, arterial thromboembolic events were reported in 2% of patients on LENVIMA + everolimus vs 6% with everolimus alone (2% vs 4% grade ≥3). Discontinue following an arterial thrombotic event. The safety of resuming LENVIMA after an arterial thromboembolic event has not been established, and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months

- Across clinical studies in which 1,160 patients received LENVIMA monotherapy, hepatic failure (including fatal events) was reported in 3 patients and acute hepatitis in 1 patient. In DTC, ALT and AST increases (grade ≥3) occurred in 4% and 5% of patients on LENVIMA, respectively, vs 0% with placebo. In RCC, ALT and AST increases (grade ≥3) occurred in 3% of patients on LENVIMA + everolimus vs 2% and 0% with everolimus alone, respectively. Monitor liver function before initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Withhold dose for liver impairment grade ≥3 until resolved to grade 0, 1, or baseline. Resume at reduced dose or discontinue based on severity/persistence of hepatotoxicity. Discontinue for hepatic failure

- In DTC, proteinuria was reported in 34% of patients on LENVIMA vs 3% with placebo (11% vs 0% grade 3). In RCC, proteinuria was reported in 31% of patients on LENVIMA + everolimus vs 14% with everolimus alone (8% vs 2% grade 3). Monitor for proteinuria before and during treatment. Withhold dose for proteinuria ≥2 g/24 h. Resume at reduced dose when proteinuria is <2 g/24 h. Discontinue for nephrotic syndrome

- In RCC, diarrhea was reported in 81% of patients on LENVIMA + everolimus vs 34% with everolimus alone (19% vs 2% grade ≥3). Initiate prompt medical management for the development of diarrhea. Monitor for dehydration. Withhold dose for diarrhea grade ≥3. Resume at a reduced dose when diarrhea resolves to grade 1 or baseline. Permanently discontinue LENVIMA for grade 4 diarrhea despite medical management

- In DTC, events of renal impairment were reported in 14% of patients on LENVIMA vs 2% with placebo (3% vs 1% grade ≥3). In RCC, events of renal impairment were reported in 18% of patients on LENVIMA + everolimus vs 12% with everolimus alone (10% vs 2% grade ≥3). Withhold LENVIMA for grade 3 or 4 renal failure/impairment. Resume at reduced dose or discontinue, depending on severity/persistence of renal impairment. Active management of diarrhea and any other gastrointestinal (GI) symptoms should be initiated for grade 1 events

- In DTC, events of GI perforation or fistula were reported in 2% of patients on LENVIMA vs 0.8% with placebo. In RCC, events of GI perforation, abscess, or fistula (grade ≥3) were reported in 2% of patients on LENVIMA + everolimus vs 0% with everolimus alone. Discontinue in patients who develop GI perforation or life-threatening fistula
In DTC, QT/QTc interval prolongation was reported in 9% of patients on LENVIMA vs 2% with placebo (2% vs 0% >500 ms). In RCC, QTc interval increases >60 ms were reported in 11% of patients on LENVIMA + everolimus (6% >500 ms) vs 0% with everolimus alone. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or patients taking drugs known to prolong the QT interval. Monitor and correct electrolyte abnormalities in all patients. Withhold dose for QTc interval prolongation >500 ms. Resume at reduced dose when QTc prolongation resolves to baseline.

In DTC, hypocalcemia (grade ≥3) was reported in 9% of patients on LENVIMA vs 2% with placebo. In RCC, hypocalcemia (grade ≥3) was reported in 6% of patients on LENVIMA + everolimus vs 0% with everolimus alone. Monitor blood calcium levels at least monthly and replace calcium as necessary. Interrupt and adjust LENVIMA as necessary.

Across clinical studies in which 1,160 patients received LENVIMA monotherapy, reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 4 patients. Withhold LENVIMA for RPLS until fully resolved. Resume at reduced dose or discontinue based on the severity and persistence of neurologic symptoms.

Across clinical studies in which 1,160 patients received LENVIMA monotherapy, hemorrhage (grade ≥3) was reported in 2% of patients. In DTC, hemorrhagic events occurred in 35% of patients on LENVIMA vs 18% with placebo (2% vs 3% grade ≥3). There was 1 fatal intracranial hemorrhage case among 16 patients who received LENVIMA and had central nervous system metastases at baseline. The most frequently reported hemorrhagic event was epistaxis (11% grade 1, 1% grade 2). Discontinuation due to hemorrhagic events occurred in 1% of patients on LENVIMA. In RCC, hemorrhagic events occurred in 34% of patients on LENVIMA + everolimus vs 26% with everolimus alone (8% vs 2% grade ≥3). The most frequently reported hemorrhagic event was epistaxis (23% for LENVIMA + everolimus vs 24% with everolimus alone). There was 1 fatal cerebral hemorrhage case. Discontinuation due to hemorrhagic events occurred in 3% of patients on LENVIMA + everolimus. Consider the risk of severe or fatal hemorrhage associated with tumor invasion/infiltration of major blood vessels (eg, carotid artery). Withhold LENVIMA for the development of grade 3 hemorrhage until resolved to grade 0 or 1. Resume at reduced dose or discontinue based on severity/persistence of hemorrhage. Discontinue for grade 4 hemorrhage.

In DTC patients with normal baseline thyroid-stimulating hormone (TSH), elevation of TSH level above 0.5 mIU/L was observed postbaseline in 57% of patients on LENVIMA vs 14% with placebo. In RCC, grade 1 or 2 hypothyroidism occurred in 24% of patients on LENVIMA + everolimus vs 2% with everolimus alone. In RCC patients with normal or low TSH at baseline, elevation of TSH was observed postbaseline in 60% of patients on LENVIMA + everolimus vs 3% with everolimus alone. Monitor thyroid function before initiation of and at least monthly throughout treatment. Treat hypothyroidism according to standard medical practice to maintain a euthyroid state.

LENVIMA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 2 weeks following completion of therapy.

Adverse Reactions

In DTC, the most common adverse reactions (≥30%) observed in LENVIMA-treated patients vs placebo-treated patients were hypertension (73% vs 16%), fatigue (67% vs 35%), diarrhea (67% vs 17%), arthralgia/myalgia (62% vs 28%), decreased appetite (54% vs 18%), weight decrease (51% vs 15%), nausea (47% vs 25%), stomatitis (41% vs 8%), headache (38% vs 11%), vomiting (36% vs 15%), proteinuria (34% vs 3%), palmar-plantar erythrodysesthesia syndrome (32% vs 1%), abdominal pain (31% vs 11%), and dysphonia (31% vs 5%).

In DTC, adverse reactions led to dose reductions in 68% of patients receiving LENVIMA and in 5% of patients receiving placebo; 18% of patients discontinued LENVIMA and 5% discontinued placebo for adverse reactions. The most common adverse reactions (≥10%) resulting in dose reductions of LENVIMA were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions (≥1%) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).
In RCC, the most common adverse reactions (>30%) observed in patients treated with LENVIMA + everolimus vs everolimus alone were diarrhea (81% vs 34%), fatigue (73% vs 40%), arthralgia/myalgia (55% vs 32%), decreased appetite (53% vs 18%), vomiting (48% vs 12%), nausea (45% vs 16%), stomatitis/oral inflammation (44% vs 50%), hypertension/increased blood pressure (42% vs 10%), peripheral edema (42% vs 20%), cough (37% vs 30%), abdominal pain (37% vs 8%), dyspnea/exertional dyspnea (35% vs 28%), rash (35% vs 40%), weight decreased (34% vs 8%), hemorrhagic events (32% vs 26%), and proteinuria/urine protein present (31% vs 14%). The most common serious adverse reactions (≥5%) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%).

In RCC, adverse reactions led to dose reductions or interruption in 89% of patients receiving LENVIMA + everolimus and in 54% of patients receiving everolimus alone. The most common adverse reactions (≥5%) resulting in dose reductions in the LENVIMA + everolimus–treated group were diarrhea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%). Treatment discontinuation due to an adverse reaction occurred in 29% of patients in the LENVIMA + everolimus–treated group and in 12% of patients in the everolimus–treated group.

Use in Specific Populations

- Because of the potential for serious adverse reactions in nursing infants, advise women to discontinue breastfeeding during treatment.
- LENVIMA may result in reduced fertility in females of reproductive potential and may result in damage to male reproductive tissues, leading to reduced fertility of unknown duration.

For more information about Lenvima, click here for the full Prescribing Information.

About Eisai Inc.

At Eisai Inc., human health care (hhc) is our goal. We give our first thought to patients and their families, and helping to increase the benefits health care provides. As the U.S. pharmaceutical subsidiary of Tokyo-based Eisai Co., Ltd., we have a passionate commitment to patient care that is the driving force behind our efforts to discover and develop innovative therapies to help address unmet medical needs.

Eisai is a fully integrated pharmaceutical business that operates in two global business groups: oncology and neurology (dementia-related diseases and neurodegenerative diseases). Each group functions as an end-to-end global business with discovery, development, and marketing capabilities. Our U.S. headquarters, commercial and clinical development organizations are located in New Jersey; our discovery labs are in Massachusetts and Pennsylvania; and our global demand chain organization resides in Maryland and North Carolina. To learn more about Eisai Inc., please visit us at eisai.com/US.

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