Eisai Data at ASCO 2017 Annual Meeting Showcase Latest Results of Ongoing Research in Oncology

- Full results of Study 304, a Phase 3 study evaluating the safety and efficacy of Lenvima® (lenvatinib) as compared to sorafenib in the first-line treatment of patients with unresectable hepatocellular carcinoma, to be presented in an oral presentation on Sunday, June 4 at 8:12 a.m. CDT

- Additional data to be presented include results from first evaluable cohort (metastatic endometrial carcinoma) of Study 111, a Phase 1b/2 trial evaluating Lenvima in combination with pembrolizumab in selected solid tumors on Saturday, June 3 from 1:15-4:45 p.m. CDT

Woodcliff Lake, NJ, May 18, 2017 – Eisai Inc. announced today the presentation of new data and analyses at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting from June 3 – 7 in Chicago. The data to be presented highlight the company’s commitment to understanding the potential of its therapies in the treatment of a variety of difficult-to-treat cancers. Notably, full results from the REFLECT trial (Study 304), a Phase 3 study evaluating Lenvima® (lenvatinib) for the first-line treatment of patients with unresectable hepatocellular carcinoma (uHCC) compared to sorafenib, will be featured in an oral presentation (Abstract #4001).

“We are proud to share our latest findings from research in patients with unresectable hepatocellular carcinoma and metastatic endometrial cancer,” said Alton Kremer, MD, PhD, Chief Clinical Officer and Chief Medical Officer, Oncology Business Group at Eisai. “Our data at ASCO include new insights into the potential of Lenvima to provide clinically meaningful improvements to patients, both as a single-agent and in combination with an immunotherapy. We look forward to ongoing discussion about the significance of these data at this important gathering.”

Additional presentations of interest include:

- Results from the cohort of patients with metastatic endometrial cancer in the Phase 1b/2 study evaluating lenvatinib in combination with pembrolizumab—the first evaluable cohort from this study of approximately 250 patients with select solid tumors.
  - Updated results of this analysis will be presented in a poster session on June 3 (Abstract #5598/Poster #420).

- A single-agent dose-finding cohort of a Phase 1/2 study of lenvatinib in children and adolescents with refractory or relapsed tumors. Patients in this trial were 2 to 18 years old and had received less than two prior VEGF-targeted therapies.

Results from the national claims database analysis, “Second or none: Many patients treated for refractory differentiated thyroid cancer with small molecular kinase inhibitors do not receive a second line of therapy,” were accepted for publication only and are available at abstract.asco.org (Abstract #e17589).
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.

The full list of Eisai presentations, including the time and location of each session, is included below.

<table>
<thead>
<tr>
<th>Abstract Name</th>
<th>Session (All times are Central)</th>
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<tr>
<td><strong>Phase 3 trial of lenvatinib vs sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma (uHCC)</strong></td>
<td>Abstract #4001</td>
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<td>Oral presentation</td>
<td>Oral: 8:12-8:24 a.m.</td>
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<td>Sunday, June 4, 2017</td>
<td>Location: Hall D2</td>
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<td>Ann-Li Cheng, MD, PhD</td>
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<td><strong>A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with endometrial carcinoma</strong></td>
<td>Abstract #5598/Poster Board #420</td>
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<td>Poster session</td>
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<td>Saturday, June 3, 2017</td>
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<td>Vicky Makker, MD</td>
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<td><strong>Single-agent dose-finding cohort of a phase 1/2 study of lenvatinib in children and adolescents with refractory or relapsed solid tumors</strong></td>
<td>Abstract #10544/Poster Board #301</td>
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<td>Poster session</td>
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<td>Nathalie Gaspar, MD</td>
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<td><strong>A phase 3 trial to compare efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab vs sunitinib alone in first-line treatment of patients with metastatic renal cell carcinoma (RCC)</strong></td>
<td>Abstract #TPS4595/Poster Board #270b</td>
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<td>Poster session</td>
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<td>Sunday, June 4, 2017</td>
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<td>Robert J. Motzer, MD</td>
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<td><strong>Validity and reliability of four value frameworks for cancer drugs</strong></td>
<td>Abstract #6603/Poster Board #425</td>
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<td>Poster session</td>
<td>Poster: 8:15-8:27 a.m.</td>
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<td>Monday, June 5, 2017</td>
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<td>Tanya G.K. Bentley, PhD</td>
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<td><strong>Chemotherapy induced nausea and vomiting in breast cancer treated with antiemetic prophylaxis as recommended by the ASCO antiemesis guidelines</strong></td>
<td>Abstract #10109/Poster Board #98</td>
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<tr>
<td>Poster session</td>
<td>Poster: 8:15-8:27 a.m.</td>
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<tr>
<td>Saturday, June 3, 2017</td>
<td>Location: Hall A</td>
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<td>Ronda Copher, PhD</td>
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**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 FGF1-4; 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.
Important 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, bradycardias, 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 RCC, hypocalcemia (grade ≥3) was reported in 9% of patients on Lenvima vs 2% with placebo. In DTC, hypocalcemia (grade ≥3) was reported in 6% of patients on Lenvima + everolimus vs 2% 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 mU/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* is our goal. We give our first thoughts 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, manufacturing 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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