Eisai and Merck Receive Breakthrough Therapy Designation from FDA for LENVIMA® (lenvatinib mesylate) and KEYTRUDA® (pembrolizumab) as Combination Therapy for Advanced and/or Metastatic Renal Cell Carcinoma

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TOKYO and KENILWORTH, N.J. - Eisai Co., Ltd. and Merck (NYSE:MRK), known as MSD outside the United States and Canada, announced today that they received Breakthrough Therapy Designation from the U.S. Food and Drug Administration (FDA) for Eisai's multiple receptor tyrosine kinase inhibitor LENVIMA® (lenvatinib) in combination with Merck's anti-PD-1 therapy KEYTRUDA® (pembrolizumab) for the potential treatment of patients with advanced and/or metastatic renal cell carcinoma (RCC). The LENVIMA and KEYTRUDA combination therapy is being jointly developed by Eisai and Merck. This is the second Breakthrough Therapy Designation for LENVIMA and the twelfth Breakthrough Therapy Designation granted to KEYTRUDA.

The Breakthrough Therapy Designation is an FDA program intended to expedite development and review of drugs for serious or life-threatening conditions. In order to qualify for this designation, preliminary clinical evidence must demonstrate that the drug may provide substantial improvement over currently available therapy on at least one clinically significant endpoint. The benefits of this Breakthrough Therapy Designation include more intensive guidance on an efficient drug development program, access to a regulatory liaison to help accelerate review time and eligibility for rolling review as well as priority review.

This Breakthrough Therapy Designation was based on the results of the RCC cohort in Study 111, a multicenter, open-label phase 1b/2 clinical study being carried out in the U.S. and the European Union (EU) to evaluate the efficacy and safety of LENVIMA in combination with KEYTRUDA in subjects with selected solid tumors.

Dr. Takashi Owa, vice president, chief medicine creation officer, oncology business group, Eisai, commented: "We are encouraged that the FDA has recognized the potential of LENVIMA plus KEYTRUDA for patients with advanced and/or metastatic renal cell carcinoma with the Breakthrough Therapy Designation. As a human health care company dedicated to giving our first thought to patients, we are committed to working closely with Merck and the FDA to expedite this clinical program with the hope that we may offer another important option for patients in need."

"The FDA's Breakthrough Therapy Designation for the LENVIMA and KEYTRUDA combination in advanced and/or metastatic renal cell carcinoma provides us with the opportunity to accelerate our effort to bring an important potential treatment option to these patients," said Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research Laboratories. "We remain committed to understanding the full potential of KEYTRUDA across cancers and treatment settings, and our collaboration with Eisai is one of the many ways we are executing on this commitment to helping more patients."

The combination of LENVIMA (lenvatinib) and KEYTRUDA (pembrolizumab) is investigational. The efficacy and safety of this combination has not been established.

About Study 111

Study 111 is a multicenter, open-label phase 1b/2 clinical study being carried out in the U.S. and EU to evaluate the efficacy and safety of LENVIMA in combination with KEYTRUDA. The primary objective of the phase 1b part was to determine the maximum tolerated dose. Patients with unresectable solid tumors (renal cell carcinoma, endometrial cancer, non-small cell lung cancer, urothelial cancer, squamous cell head and neck cancer and melanoma) who had progressed after treatment with approved therapies or for which there are no standard effective therapies available were administered 24 mg of LENVIMA orally daily, as well as 200 mg of KEYTRUDA intravenously every three weeks. Dose reductions of LENVIMA were permitted based on observed toxicity. The phase 2 part was conducted with patients who had select solid tumors with 0-2 prior lines of systemic therapy (unless discussed with the sponsor), with a recommended dosage of 20 mg of LENVIMA daily and 200 mg of KEYTRUDA every three weeks as determined based on the results of the phase 1b part. The primary endpoint of the phase 2 part was objective response rate at 24 weeks after treatment began, with select secondary endpoints including objective response rate, disease control rate, progression-free survival and duration of response. Currently, the phase 2 part is underway, with enrollment expanded for the endometrial cancer cohort.
About Renal Cell Carcinoma

In 2012, the number of patients with renal cancer was estimated to be approximately 338,000 worldwide, including approximately 58,000 in the US, 115,000 in Europe and 17,000 in Japan. In the US, approximately 63,990 new cases were estimated to occur in 2017. Approximately 25–30 percent of patients are estimated to present with metastatic disease at time of diagnosis. Renal cell carcinoma comprises approximately 90 percent of all malignancies of the kidney, and originates from malignant cells in the lining of the tubules of the kidney. The average age of a renal cancer diagnosis is 64, and it is more likely to affect men than women. For advanced or metastatic renal cell carcinoma that is difficult to treat with surgery, the standard treatment is molecular targeted drug therapy. However, this remains a disease with significant unmet medical need.

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.

LENVIMA, 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 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). LENVIMA also inhibits other RTKs that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their vascular endothelial growth factor (FGF) receptors FGFRI-4; the platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. The combination of LENVIMA 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 (lenvatinib) 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). Serious complications of poorly controlled hypertension, including aortic dissection, have been reported. 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 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 hepatic toxicity. 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). Discontinue for 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 (lenvatinib) + 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 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.

- 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).

- 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.

- Impaired wound healing, including fistula formation, has been reported in patients receiving LENVIMA. Temporary interruption of LENVIMA therapy should be considered in patients undergoing major surgical procedures.

- 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 (lenvatinib) 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 (36% vs 15%), dyspnea (35% vs 4%), rash (35% vs 4%), weight decreased (34% vs 8%), hypothyroidism (32% vs 1%), abdominal pain (31% vs 1%), headache (30% vs 11%), and dyspnea (30% vs 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 (≥30%) observed in patients treated with LENVIMA 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%).

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### 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 KEYTRUDA® (pembrolizumab) Injection, 100 mg

KEYTRUDA is an anti-PD-1 therapy that works by increasing the activity 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 has the industry's largest immuno-oncology clinical research program, which currently involves more than 650 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 benefiting from treatment with KEYTRUDA, including exploring several different biomarkers.

### KEYTRUDA (pembrolizumab) Indications and Dosing in the U.S.
KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma at a fixed dose of 200 mg every three weeks until disease progression or unacceptable toxicity.

**Lung Cancer**

KEYTRUDA (pembrolizumab), as a single agent, is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [tumor proportion score (TPS) ≥50%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, as a single agent, is also indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

KEYTRUDA is also indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. In HNSCC, KEYTRUDA is administered at a fixed dose of 200 mg every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

When administering KEYTRUDA in combination with chemotherapy, KEYTRUDA should be administered prior to chemotherapy when given on the same day. See also the Prescribing Information for pemetrexed and carboplatin.

**Head and Neck Cancer**

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. In HNSCC, KEYTRUDA is administered at a fixed dose of 200 mg every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

**Classical Hodgkin Lymphoma**

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after three or more prior lines of therapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

KEYTRUDA is also indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. In locally advanced or metastatic urothelial carcinoma, KEYTRUDA (pembrolizumab) is administered at a fixed dose of 200 mg every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

**Microsatellite Instability-High (MSI-H) Cancer**

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

In adult patients with MSI-H cancer, KEYTRUDA is administered at a fixed dose of 200 mg every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. In children with MSI-H cancer, KEYTRUDA is administered at a dose of 2 mg/kg (up to a maximum of 200 mg) every three weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.
KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The recommended dose of KEYTRUDA is 200 mg every three weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Selected Important Safety Information for KEYTRUDA® (pembrolizumab)

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%) pneumonitis, and occurred more frequently in patients with a history of prior thoracic radiation (6.9%) compared to those without (2.9%). Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

KEYTRUDA can cause immune-mediated colitis. Colitis occurred in 48 (1.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.4%), 3 (1.1%), and 4 (<0.1%) colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA for Grade 4 colitis.

KEYTRUDA can cause immune-mediated hepatitis. Hepatitis occurred in 19 (0.7%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%) hepatitis. Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA (pembrolizumab).

KEYTRUDA can cause hypophysitis. Hypophysitis occurred in 17 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%) hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2; withhold or discontinue for Grade 3 or 4 hypophysitis.

KEYTRUDA can cause thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis. Hyperthyroidism occurred in 96 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.8%) and 3 (0.1%) hyperthyroidism. Hypothyroidism occurred in 237 (8.5%) of 2799 patients receiving KEYTRUDA, including Grade 2 (6.2%) and 3 (0.1%) hypothyroidism. The incidence of new or worsening hyperthyroidism was higher in patients with HNSCC, occurring in 28 (15%) of 192 patients with HNSCC, including Grade 3 (0.5%) hyperthyroidism. Thyroiditis occurred in 16 (0.6%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.3%) thyroiditis. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for Grade 3 or 4 hyperthyroidism.

KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer antihyperglycemics in patients with severe hyperglycemia.

KEYTRUDA can cause immune-mediated nephritis. Nephritis occurred in 9 (0.3%) of 2799 patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.1%), and 4 (<0.1%) nephritis. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 nephritis.

Immune-mediated rashes, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA.

KEYTRUDA can cause other clinically important immune-mediated adverse reactions. These immune-mediated reactions may occur in any organ system. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

The following clinically significant immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, and partial seizures arising in a patient with inflammatory foci in brain parenchyma. In addition, myelitis and myocardiitis were reported in other clinical trials, including classical Hodgkin lymphoma, and postmarketing use.

Solid organ transplant rejection has been reported in postmarketing use of KEYTRUDA (pembrolizumab). Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA vs the risk of possible organ rejection in these patients.
KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients. Monitor patients for signs and symptoms of infusion-related reactions, including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For Grade 3 or 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA. Of 23 patients with cHL who proceeded to allogeneic HSCT after treatment with KEYTRUDA on any trial, 6 patients (26%) developed graft-versus-host disease (GVHD), one of which was fatal, and 2 patients (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning, one of which was fatal. Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor-blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

In clinical trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with a PD-1 or PD-L1 blocking antibody in this combination is not recommended outside of controlled clinical trials.

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. If used during pregnancy, or if the patient becomes pregnant during treatment, apprise the patient of the potential hazard to a fetus. Advise females of reproductive potential to use highly effective contraception during treatment and for 4 months after the last dose of KEYTRUDA.

In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions with KEYTRUDA vs ipilimumab were fatigue (28% vs 28%), diarrhea (26% with KEYTRUDA), rash (24% vs 23%), and nausea (21% with KEYTRUDA). Corresponding incidence rates are listed for ipilimumab only for those adverse reactions that occurred at the same or lower rate than with KEYTRUDA.

In KEYNOTE-010, KEYTRUDA monotherapy was discontinued due to adverse reactions in 8% of 682 patients with metastatic NSCLC. The most common adverse event resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.8%). Adverse reactions leading to interruption of KEYTRUDA occurred in 23% of patients; the most common (≥1%) were diarrhea (1%), fatigue (1.3%), pneumonia (1%), liver enzyme elevation (1.2%), decreased appetite (1.3%), and pneumonitis (1%). The most common adverse reactions (occurring in at least 20% of patients and at a higher incidence than with docetaxel) were decreased appetite (25% vs 23%), dyspnea (23% vs 20%), and nausea (20% vs 18%).

In KEYNOTE-021(G1), when KEYTRUDA (pembrolizumab) was administered in combination with carboplatin and pemetrexed (carbo/pem) in advanced nonsquamous NSCLC, KEYTRUDA was discontinued in 10% of 59 patients. The most common adverse reaction resulting in discontinuation of KEYTRUDA (≥2%) was acute kidney injury (3.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 39% of patients; the most common (≥2%) were fatigue (8%), neutrophil count decreased (8%), anemia (5%), dyspnea (3.4%), and pneumonitis (3.4%). The most common adverse reactions (≥20%) with KEYTRUDA compared to carbo/pem alone were fatigue (71% vs 50%), nausea (68% vs 56%), constipation (51% vs 37%), rash (42% vs 21%), vomiting (39% vs 27%), dyspnea (39% vs 21%), diarrhea (37% vs 23%), decreased appetite (31% vs 23%), headache (31% vs 16%), cough (24% vs 18%), dizziness (24% vs 16%), insomnia (24% vs 15%), pruritus (24% vs 4.8%), peripheral edema (22% vs 18%), dysgeusia (20% vs 11%), alopecia (20% vs 3.2%), upper respiratory tract infection (20% vs 3.2%), and arthralgia (15% vs 24%). This study was not designed to demonstrate a statistically significant difference in adverse reaction rates for KEYTRUDA as compared to carbo/pem alone for any specified adverse reaction.

In KEYNOTE-012, KEYTRUDA was discontinued due to adverse reactions in 17% of 192 patients with HNSCC. Serious adverse reactions occurred in 45% of patients. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspepsia, confusional state, vomiting, pleural effusion, and respiratory failure. The most common adverse reactions (reported in at least 20% of patients) were fatigue, decreased appetite, and dyspepsia. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3 or 4) and new or worsening hypothyroidism.

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 5% of 210 patients with cHL, and treatment was interrupted due to adverse reactions in 26% of patients. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspepsia, GVHD, and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with locally advanced or metastatic urothelial carcinoma. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). The most common adverse reactions...
(≥20%) in patients who received KEYTRUDA vs those who received chemotherapy were fatigue (38% vs 56%), musculoskeletal pain (32% vs 27%), pruritus (23% vs 6%), decreased appetite (21% vs 21%), nausea (21% vs 29%), and rash (20% vs 13%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients, the most frequent (≥2%) of which were urinary tract infection, pneumonia, anemia, and pneumonitis.

It is not known whether KEYTRUDA (pembrolizumab) is excreted in human milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

There is limited experience in pediatric patients. In a study, 40 pediatric patients (16 children aged 2 years to younger than 12 years and 24 adolescents aged 12 years to 18 years) with advanced melanoma, lymphoma, or PD-L1-positive advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range 1–17 doses), with 34 patients (85%) receiving KEYTRUDA for 2 doses or more. The safety profile in these pediatric patients was similar to that seen in adults treated with KEYTRUDA. Toxocities that occurred at a higher rate (≥15% difference) in these patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), hypertransaminasemia (28%), and hyponatremia (18%).


About Eisai Co., Ltd.

Eisai Co., Ltd. is a leading global research and development-based pharmaceutical company headquartered in Japan. 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. With over 10,000 employees working across our global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realize our hhc philosophy by delivering innovative products in various therapeutic areas with high unmet medical needs, including Oncology and Neurology.

As a global pharmaceutical company, our mission extends to patients around the world through our investment and participation in partnership-based initiatives to improve access to medicines in developing and emerging countries.

For more information about Eisai Co., Ltd., please visit www.eisai.com.

Merck's Focus on Cancer

Merck's goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, helping people fight cancer is our passion and supporting accessibility to our cancer medicines is our commitment. Our focus is on pursuing research in immuno-oncology and we are accelerating every step in the journey – from lab to clinic – to potentially bring new hope to people with cancer.

As part of our focus on cancer, Merck is committed to exploring the potential of immuno-oncology with one of the fastest-growing development programs in the industry. We are currently executing an expansive research program evaluating our anti-PD-1 therapy across more than 30 tumor types. We also continue to strengthen our immuno-oncology portfolio through strategic acquisitions and are prioritizing the development of several promising immunotherapeutic 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

For more than a century, Merck, a leading global biopharmaceutical company 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. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola.

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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 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 approvals; 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 2016 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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