



NEWS RELEASE

Merck and Eisai Provide Update on Phase 3 LEAP-002 Trial Evaluating KEYTRUDA® (pembrolizumab) Plus LENVIMA® (lenvatinib) Versus LENVIMA Monotherapy in Patients With Unresectable Hepatocellular Carcinoma

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RAHWAY, N.J. & NUTLEY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, and Eisai today announced that the Phase 3 LEAP-002 trial investigating KEYTRUDA, Merck's anti-PD-1 therapy, plus LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, versus LENVIMA monotherapy did not meet its dual primary endpoints of overall survival (OS) and progression-free survival (PFS) as a first-line treatment for patients with unresectable hepatocellular carcinoma (uHCC). There were trends toward improvement in OS and PFS for patients who received KEYTRUDA plus LENVIMA versus LENVIMA monotherapy; however, these results did not meet statistical significance per the pre-specified statistical plan. The median OS of the LENVIMA monotherapy arm in LEAP-002 was longer than that observed in previously reported clinical trials evaluating LENVIMA monotherapy in uHCC. The safety profile of KEYTRUDA plus LENVIMA was consistent with previously reported data on the combination. Merck and Eisai plan to present these data at an upcoming medical conference.

This press release features multimedia. View the full release here:

<https://www.businesswire.com/news/home/20220803005211/en/>

"Our joint clinical development program for KEYTRUDA plus LENVIMA is designed to address unmet needs for some of the most challenging-to-treat types of cancer, like hepatocellular carcinoma," said Dr. Gregory Lubiniecki, Vice

President, Global Clinical Development, Merck Research Laboratories. “We remain confident in the potential of this combination based on the body of evidence we’ve seen to date and will continue to investigate its role across multiple types of cancer.”

“Aiming for further improvement in the treatment of patients with unresectable HCC, we selected LENVIMA monotherapy, a standard of care option, as the control arm of the LEAP-002 trial,” said Corina Dutcus, M.D., Senior Vice President, Clinical Research, Oncology at Eisai Inc. “While results evaluating the combination are not what we had hoped for, we will continue to contribute to the care of patients with unresectable HCC by applying valuable knowledge from the LEAP-002 trial.”

LENVIMA monotherapy is approved for the first-line treatment of patients with uHCC in the U.S., Europe, and China, and for patients with uHCC in Japan. The approval of LENVIMA was based on results of the Phase 3 REFLECT trial which evaluated the efficacy and safety of LENVIMA versus sorafenib for the first-line treatment of patients with uHCC.

In the U.S., KEYTRUDA plus LENVIMA is approved for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high or mismatch repair deficient, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation and for adult patients with advanced renal cell carcinoma (RCC) in the first-line setting. In Europe, KEYTRUDA plus LENVIMA (marketed as KISPLYX® for RCC in the EU) is approved for adult patients with advanced or recurrent endometrial carcinoma who have disease progression on or following prior treatment with a platinum containing therapy in any setting and are not candidates for curative surgery or radiation and for adults with advanced RCC in the first-line setting. The KEYTRUDA plus LENVIMA combination is also approved in Japan for patients with radically unresectable or metastatic RCC and patients with unresectable, advanced or recurrent endometrial carcinoma that progressed after cancer chemotherapy. Results from the LEAP-002 trial do not affect the current approved indications for the KEYTRUDA plus LENVIMA combination.

Merck and Eisai are studying the KEYTRUDA plus LENVIMA combination through the LEAP (LEnvatinib And Pembrolizumab) clinical program in more than 10 different tumor types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, head and neck cancer, biliary tract cancer, colorectal cancer, gastric cancer, esophageal cancer, glioblastoma and pancreatic cancer) across more than 15 clinical trials.

About LEAP-002

LEAP-002 is a multicenter, randomized, double-blinded, active-controlled Phase 3 trial ([ClinicalTrials.gov, NCT03713593](https://clinicaltrials.gov/ct2/show/study/NCT03713593)) evaluating KEYTRUDA plus LENVIMA versus LENVIMA monotherapy for the first-line treatment of

adult patients with uHCC. The dual primary endpoints are PFS, as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors Version (RECIST) v1.1 (RECIST v1.1 has been modified for this study to follow a maximum of 10 target lesions in total and a maximum of 5 target lesions per organ), and OS. The secondary endpoints include objective response rate (ORR), as assessed by BICR per RECIST v1.1, and duration of response (DOR). The study enrolled 794 patients who were randomized 1:1 to receive:

- KEYTRUDA (200 mg intravenously [IV] on Day 1 of each three-week cycle) plus LENVIMA (12 mg orally once daily [for patients with screening body weight of at least 60 kg] or 8 mg orally once daily [for patients with screening body weight less than 60 kg]); or
- LENVIMA (12 mg orally once daily [for patients with screening body weight of at least 60 kg] or 8 mg orally once daily [for patients with screening body weight less than 60 kg]) plus saline placebo (IV administered on Day 1 of each three-week cycle).

LENVIMA was administered until progressive disease or unacceptable toxicity. KEYTRUDA/placebo was administered for up to 35 cycles (approximately two years).

About hepatocellular carcinoma (HCC)

Hepatocellular carcinoma is the most common type of primary liver cancer and the most rapidly increasing cause of cancer deaths in the United States. Hepatocellular carcinoma accounts for approximately 90% of primary liver cancers. It is estimated there were more than 905,000 new cases of liver cancer and more than 830,000 deaths from the disease globally in 2020, making it the sixth most frequently diagnosed cancer worldwide and one of the leading causes of cancer deaths around the world. In the United States, it is estimated there will be over 41,000 new cases of liver cancer and over 30,000 deaths from this disease in 2022. Risk factors for liver cancer include gender, ethnicity, chronic viral hepatitis (Hep-B or Hep-C) infection, cirrhosis, alcohol use and metabolic syndrome. Hepatocellular carcinoma, which is often diagnosed at an advanced stage, has a five-year survival rate of approximately 20% in the U.S.

About KEYTRUDA® (pembrolizumab) injection, 100 mg

KEYTRUDA is an anti-programmed death receptor-1 (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 has the industry's largest immuno-oncology clinical research program. There are currently more than 1,600 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.

Selected KEYTRUDA® (pembrolizumab) Indications in the U.S.

Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. 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.

See additional selected KEYTRUDA indications in the U.S. after the Selected Important Safety Information.

Selected Important Safety Information for KEYTRUDA

Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the PD-1 or the PD-L1, blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, can affect more than one body system simultaneously, and can occur at any time after starting treatment or after discontinuation of treatment. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.

Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Early identification and management are essential to ensure safe use of anti-PD-1/PD-L1 treatments. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. For patients with TNBC treated with KEYTRUDA in the neoadjuvant setting, monitor blood cortisol at baseline, prior to surgery, and as clinically indicated. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less,

initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis. The incidence is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) reactions. Systemic corticosteroids were required in 67% (63/94) of patients. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) and withholding in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

Pneumonitis occurred in 8% (31/389) of adult patients with cHL receiving KEYTRUDA as a single agent, including Grades 3-4 in 2.3% of patients. Patients received high-dose corticosteroids for a median duration of 10 days (range: 2 days to 53 months). Pneumonitis rates were similar in patients with and without prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 5.4% (21) of patients. Of the patients who developed pneumonitis, 42% interrupted KEYTRUDA, 68% discontinued KEYTRUDA, and 77% had resolution.

Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) reactions. Systemic corticosteroids were required in 69% (33/48); additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) and withholding in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Colitis resolved in 85% of the 48 patients.

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 68% (13/19) of patients; additional immunosuppressant therapy was required in 11% of patients. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) and withholding in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Hepatitis resolved in 79% of the 19 patients.

KEYTRUDA With Axitinib

KEYTRUDA in combination with axitinib can cause hepatic toxicity. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider monitoring more frequently as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib, and consider administering corticosteroids as needed. With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased alanine aminotransferase (ALT) (20%) and increased aspartate aminotransferase (AST) (13%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥ 3 times upper limit of normal (ULN) (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT ≥ 3 times ULN was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT ≥ 3 ULN subsequently recovered from the event.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

KEYTRUDA can cause primary or secondary adrenal insufficiency. For Grade 2 or higher, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity. Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) reactions. Systemic corticosteroids were required in 77% (17/22) of patients; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hypophysitis

KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Thyroid Disorders

KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). None discontinued, but KEYTRUDA was withheld in <0.1% (1) of patients.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). It led to permanent discontinuation of KEYTRUDA in <0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in <0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in 389 adult patients with cHL (17%) receiving KEYTRUDA as a single agent, including Grade 1 (6.2%) and Grade 2 (10.8%) hypothyroidism.

Type 1 Diabetes Mellitus (DM), Which Can Present With Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity. Type 1 DM occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 89% (8/9) of patients. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) and withholding in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence. Nephritis resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms, and toxic epidermal necrolysis, has occurred with anti-PD-1/PD-L1 treatments. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate nonexfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity. Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) reactions. Systemic corticosteroids were required in 40% (15/38) of patients. These reactions led to permanent discontinuation in 0.1% (2) and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence. The reactions resolved in 79% of the 38 patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other anti-PD-1/PD-L1 treatments. Severe or fatal cases have been reported for some of these adverse reactions. Cardiac/Vascular: Myocarditis, pericarditis, vasculitis; Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis; Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica; Endocrine: Hypoparathyroidism; Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving KEYTRUDA. Monitor for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or Grade 2 reactions. For Grade 3 or Grade 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti-PD-1/PD-L1 treatments. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti-PD-1/PD-L1 treatment and allogeneic HSCT. Follow patients closely for evidence of these complications and intervene promptly. Consider the benefit vs risks of using anti-PD-1/PD-L1 treatments prior to or after an allogeneic HSCT.

Increased Mortality in Patients With Multiple Myeloma

In 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 an anti-PD-1/PD-L1 treatment in this combination is not recommended outside of controlled trials.

Embryofetal Toxicity

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA and advise them to use effective contraception during treatment and for 4 months after the last dose.

Adverse Reactions

In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to permanent 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%). The most common adverse reactions ($\geq 20\%$) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

In KEYNOTE-054, when KEYTRUDA was administered as a single agent to patients with stage III melanoma, KEYTRUDA was permanently discontinued due to adverse reactions in 14% of 509 patients; the most common ($\geq 1\%$) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. The most common adverse reaction ($\geq 20\%$) with KEYTRUDA was diarrhea (28%). In KEYNOTE-716, when KEYTRUDA was administered as a single agent to patients with stage IIB or IIC melanoma, adverse reactions occurring in patients with stage IIB or IIC melanoma were similar to those occurring in 1011 patients with stage III melanoma from KEYNOTE-054.

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic

nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 20% of 405 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions ($\geq 20\%$) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), diarrhea (31%), decreased appetite (28%), rash (25%), vomiting (24%), cough (21%), dyspnea (21%), and pyrexia (20%).

In KEYNOTE-407, when KEYTRUDA was administered with carboplatin and either paclitaxel or paclitaxel protein-bound in metastatic squamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 15% of 101 patients. The most frequent serious adverse reactions reported in at least 2% of patients were febrile neutropenia, pneumonia, and urinary tract infection. Adverse reactions observed in KEYNOTE-407 were similar to those observed in KEYNOTE-189 with the exception that increased incidences of alopecia (47% vs 36%) and peripheral neuropathy (31% vs 25%) were observed in the KEYTRUDA and chemotherapy arm compared to the placebo and chemotherapy arm in KEYNOTE-407.

In KEYNOTE-042, KEYTRUDA was discontinued due to adverse reactions in 19% of 636 patients with advanced NSCLC; the most common were pneumonitis (3%), death due to unknown cause (1.6%), and pneumonia (1.4%). The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia (7%), pneumonitis (3.9%), pulmonary embolism (2.4%), and pleural effusion (2.2%). The most common adverse reaction ($\geq 20\%$) was fatigue (25%).

In KEYNOTE-010, KEYTRUDA monotherapy was discontinued due to adverse reactions in 8% of 682 patients with metastatic NSCLC; the most common was pneumonitis (1.8%). The most common adverse reactions ($\geq 20\%$) were decreased appetite (25%), fatigue (25%), dyspnea (23%), and nausea (20%).

In KEYNOTE-048, KEYTRUDA monotherapy was discontinued due to adverse events in 12% of 300 patients with HNSCC; the most common adverse reactions leading to permanent discontinuation were sepsis (1.7%) and pneumonia (1.3%). The most common adverse reactions ($\geq 20\%$) were fatigue (33%), constipation (20%), and rash (20%).

In KEYNOTE-048, when KEYTRUDA was administered in combination with platinum (cisplatin or carboplatin) and FU chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 16% of 276 patients with HNSCC. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). The most common adverse reactions ($\geq 20\%$) were nausea (51%), fatigue (49%), constipation (37%), vomiting (32%), mucosal inflammation (31%), diarrhea (29%), decreased appetite (29%), stomatitis (26%), and cough (22%).

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, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The most common adverse reactions ($\geq 20\%$) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy, with the exception of increased incidences of facial edema and new or worsening hypothyroidism.

In KEYNOTE-204, KEYTRUDA was discontinued due to adverse reactions in 14% of 148 patients with cHL. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA; those $\geq 1\%$ were pneumonitis, pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients died from causes other than disease progression: 2 from complications after allogeneic HSCT and 1 from unknown cause. The most common adverse reactions ($\geq 20\%$) were upper respiratory tract infection (41%), musculoskeletal pain (32%), diarrhea (22%), and pyrexia, fatigue, rash, and cough (20% each).

In KEYNOTE-087, KEYTRUDA was discontinued due to adverse reactions in 5% of 210 patients with cHL. Serious adverse reactions occurred in 16% of patients; those $\geq 1\%$ were pneumonia, pneumonitis, pyrexia, dyspnea, GVHD, and herpes zoster. Two patients died from causes other than disease progression: 1 from GVHD after subsequent allogeneic HSCT and 1 from septic shock. The most common adverse reactions ($\geq 20\%$) were fatigue (26%), pyrexia (24%), cough (24%), musculoskeletal pain (21%), diarrhea (20%), and rash (20%).

In KEYNOTE-170, KEYTRUDA was discontinued due to adverse reactions in 8% of 53 patients with PMBCL. Serious adverse reactions occurred in 26% of patients and included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. The most common adverse reactions ($\geq 20\%$) were musculoskeletal pain (30%), upper respiratory tract infection and pyrexia (28% each), cough (26%), fatigue (23%), and dyspnea (21%).

In KEYNOTE-052, KEYTRUDA was discontinued due to adverse reactions in 11% of 370 patients with locally advanced or mUC. Serious adverse reactions occurred in 42% of patients; those $\geq 2\%$ were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis. The most common adverse reactions ($\geq 20\%$) were fatigue (38%), musculoskeletal pain (24%), decreased appetite (22%), constipation (21%), rash (21%), and diarrhea (20%).

In KEYNOTE-045, KEYTRUDA was discontinued due to adverse reactions in 8% of 266 patients with locally advanced or mUC. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients; those $\geq 2\%$ were urinary tract infection, pneumonia, anemia, and pneumonitis. The most common adverse reactions ($\geq 20\%$) in patients who received KEYTRUDA were fatigue (38%), musculoskeletal pain (32%), pruritus (23%), decreased

appetite (21%), nausea (21%), and rash (20%).

In KEYNOTE-057, KEYTRUDA was discontinued due to adverse reactions in 11% of 148 patients with high-risk NMIBC. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Serious adverse reactions occurred in 28% of patients; those $\geq 2\%$ were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). The most common adverse reactions ($\geq 20\%$) were fatigue (29%), diarrhea (24%), and rash (24%).

Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-811, when KEYTRUDA was administered in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, KEYTRUDA was discontinued due to adverse reactions in 6% of 217 patients with locally advanced unresectable or metastatic HER2+ gastric or GEJ adenocarcinoma. The most common adverse reaction resulting in permanent discontinuation was pneumonitis (1.4%). In the KEYTRUDA arm versus placebo, there was a difference of $\geq 5\%$ incidence between patients treated with KEYTRUDA versus standard of care for diarrhea (53% vs 44%) and nausea (49% vs 44%).

The most common adverse reactions (reported in $\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, and insomnia.

In KEYNOTE-590, when KEYTRUDA was administered with cisplatin and fluorouracil to patients with metastatic or locally advanced esophageal or GEJ (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation, KEYTRUDA was discontinued due to adverse reactions in 15% of 370 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA ($\geq 1\%$) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). The most common adverse reactions ($\geq 20\%$) with KEYTRUDA in combination with chemotherapy were nausea (67%), fatigue (57%), decreased appetite (44%), constipation (40%), diarrhea (36%), vomiting (34%), stomatitis (27%), and weight loss (24%).

Adverse reactions occurring in patients with esophageal cancer who received KEYTRUDA as a monotherapy were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-826, when KEYTRUDA was administered in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab (n=307), to patients with persistent, recurrent, or first-line metastatic

cervical cancer regardless of tumor PD-L1 expression who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent, fatal adverse reactions occurred in 4.6% of patients, including 3 cases of hemorrhage, 2 cases each of sepsis and due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection. Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab; those $\geq 3\%$ were febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), and acute kidney injury and sepsis (3.3% each).

KEYTRUDA was discontinued in 15% of patients due to adverse reactions. The most common adverse reaction resulting in permanent discontinuation ($\geq 1\%$) was colitis (1%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common adverse reactions ($\geq 20\%$) were peripheral neuropathy (62%), alopecia (58%), anemia (55%), fatigue/asthenia (53%), nausea and neutropenia (41% each), diarrhea (39%), hypertension and thrombocytopenia (35% each), constipation and arthralgia (31% each), vomiting (30%), urinary tract infection (27%), rash (26%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (21%).

For patients treated with KEYTRUDA in combination with chemotherapy with or without bevacizumab, the most common adverse reactions ($\geq 20\%$) were peripheral neuropathy (58%), alopecia (56%), fatigue (47%), nausea (40%), diarrhea (36%), constipation (28%), arthralgia (27%), vomiting (26%), hypertension and urinary tract infection (24% each), and rash (22%).

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with previously treated recurrent or metastatic cervical cancer. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA; the most frequent included anemia (7%), fistula, hemorrhage, and infections [except urinary tract infections] (4.1% each). The most common adverse reactions ($\geq 20\%$) were fatigue (43%), musculoskeletal pain (27%), diarrhea (23%), pain and abdominal pain (22% each), and decreased appetite (21%).

Adverse reactions occurring in patients with HCC were generally similar to those in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy, with the exception of increased incidences of ascites (8% Grades 3-4) and immune-mediated hepatitis (2.9%). Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (20%), ALT (9%), and hyperbilirubinemia (10%).

Among the 50 patients with MCC enrolled in study KEYNOTE-017, adverse reactions occurring in patients with MCC were generally similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (11%)

and hyperglycemia (19%).

In KEYNOTE-426, when KEYTRUDA was administered in combination with axitinib, fatal adverse reactions occurred in 3.3% of 429 patients. Serious adverse reactions occurred in 40% of patients, the most frequent ($\geq 1\%$) were hepatotoxicity (7%), diarrhea (4.2%), acute kidney injury (2.3%), dehydration (1%), and pneumonitis (1%). Permanent discontinuation due to an adverse reaction occurred in 31% of patients; KEYTRUDA only (13%), axitinib only (13%), and the combination (8%); the most common were hepatotoxicity (13%), diarrhea/colitis (1.9%), acute kidney injury (1.6%), and cerebrovascular accident (1.2%). The most common adverse reactions ($\geq 20\%$) were diarrhea (56%), fatigue/asthenia (52%), hypertension (48%), hepatotoxicity (39%), hypothyroidism (35%), decreased appetite (30%), palmar-plantar erythrodysesthesia (28%), nausea (28%), stomatitis/mucosal inflammation (27%), dysphonia (25%), rash (25%), cough (21%), and constipation (21%).

In KEYNOTE-581, when KEYTRUDA was administered in combination with LENVIMA to patients with advanced renal carcinoma (n=352), fatal adverse reactions occurred in 4.3% of patients. Serious adverse reactions occurred in 51% of patients, the most common ($\geq 2\%$) were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction, pneumonitis, and vomiting (3% each), acute kidney injury, adrenal insufficiency, dyspnea, and pneumonia (2% each).

Permanent discontinuation of either KEYTRUDA, LENVIMA, or both due to an adverse reaction occurred in 37% of patients; 29% KEYTRUDA only, 26% lenvatinib only, and 13% both. The most common adverse reactions ($\geq 2\%$) resulting in permanent discontinuation of KEYTRUDA, LENVIMA, or the combination were pneumonitis (3%), myocardial infarction, hepatotoxicity, acute kidney injury, and rash (3% each), and diarrhea (2%).

The most common adverse reactions ($\geq 20\%$) observed with KEYTRUDA in combination with LENVIMA were fatigue (63%), diarrhea (62%), musculoskeletal disorders (58%), hypothyroidism (57%), hypertension (56%), stomatitis (43%), decreased appetite (41%), rash (37%), nausea (36%), weight loss, dysphonia and proteinuria (30% each), palmar-plantar erythrodysesthesia syndrome (29%), abdominal pain and hemorrhagic events (27% each), vomiting (26%), constipation and hepatotoxicity (25% each), headache (23%), and acute kidney injury (21%).

In KEYNOTE-564, when KEYTRUDA was administered as a single agent for the adjuvant treatment of renal cell carcinoma, serious adverse reactions occurred in 20% of patients receiving KEYTRUDA; the serious adverse reactions ($\geq 1\%$) were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis (1% each). Fatal adverse reactions occurred in 0.2% including 1 case of pneumonia. Discontinuation of KEYTRUDA due to adverse reactions occurred in 21% of 488 patients; the most common ($\geq 1\%$) were increased ALT (1.6%), colitis (1%), and adrenal insufficiency (1%). The most common adverse reactions ($\geq 20\%$) were musculoskeletal pain (41%), fatigue (40%), rash (30%), diarrhea (27%), pruritus (23%), and hypothyroidism (21%).

In KEYNOTE-775, when KEYTRUDA was administered in combination with LENVIMA to patients with advanced endometrial carcinoma that were not MSI-H or dMMR (n=342), fatal adverse reactions occurred in 4.7% of patients. Serious adverse reactions occurred in 50% of these patients; the most common ($\geq 3\%$) were hypertension (4.4%) and urinary tract infections (3.2%).

Discontinuation of KEYTRUDA, due to an adverse reaction occurred in 15% of these patients. The most common adverse reaction leading to discontinuation of KEYTRUDA ($\geq 1\%$) was increased ALT (1.2%).

The most common adverse reactions for KEYTRUDA in combination with LENVIMA (reported in $\geq 20\%$ patients) were hypothyroidism and hypertension (67% each), fatigue (58%), diarrhea (55%), musculoskeletal disorders (53%), nausea (49%), decreased appetite (44%), vomiting (37%), stomatitis (35%), abdominal pain and weight loss (34% each), urinary tract infections (31%), proteinuria (29%), constipation (27%), headache (26%), hemorrhagic events (25%), palmar-plantar erythrodysesthesia (23%), dysphonia (22%), and rash (20%).

Adverse reactions occurring in patients with MSI-H or dMMR endometrial carcinoma who received KEYTRUDA as a single agent were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a single agent.

Adverse reactions occurring in patients with TMB-H cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

Adverse reactions occurring in patients with recurrent or metastatic cSCC or locally advanced cSCC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

In KEYNOTE-522, when KEYTRUDA was administered with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent (n=778) to patients with newly diagnosed, previously untreated, high-risk early-stage TNBC, fatal adverse reactions occurred in 0.9% of patients, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA; those $\geq 2\%$ were febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%). KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions ($\geq 1\%$) resulting in permanent discontinuation were increased ALT (2.7%), increased AST (1.5%), and rash (1%). The most common adverse reactions ($\geq 20\%$) in patients receiving KEYTRUDA were fatigue (70%), nausea (67%), alopecia (61%), rash (52%), constipation (42%), diarrhea and peripheral neuropathy (41% each), stomatitis (34%), vomiting (31%), headache (30%), arthralgia (29%), pyrexia (28%), cough (26%), abdominal pain (24%), decreased appetite (23%), insomnia (21%), and myalgia (20%).

In KEYNOTE-355, when KEYTRUDA and chemotherapy (paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin) were administered to patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting (n=596), fatal adverse reactions occurred in 2.5% of patients, including cardio-respiratory arrest (0.7%) and septic shock (0.3%). Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with chemotherapy; the serious reactions in $\geq 2\%$ were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%). KEYTRUDA was discontinued in 11% of patients due to adverse reactions. The most common reactions resulting in permanent discontinuation ($\geq 1\%$) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions ($\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue (48%), nausea (44%), alopecia (34%), diarrhea and constipation (28% each), vomiting and rash (26% each), cough (23%), decreased appetite (21%), and headache (20%).

Lactation

Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the final dose.

Pediatric Use

In KEYNOTE-051, 161 pediatric patients (62 pediatric patients aged 6 months to younger than 12 years and 99 pediatric patients aged 12 years to 17 years) were administered KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 24 months).

Adverse reactions that occurred at a $\geq 10\%$ higher rate in pediatric patients when compared to adults were pyrexia (33%), vomiting (30%), leukopenia (30%), upper respiratory tract infection (29%), neutropenia (26%), headache (25%), and Grade 3 anemia (17%).

Additional Selected KEYTRUDA Indications in the U.S.

Melanoma

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB, IIC, or III melanoma following complete resection.

Non-Small Cell Lung Cancer

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [tumor proportion score (TPS) $\geq 1\%$] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:

- stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$) 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.

Head and Neck Squamous Cell Cancer

KEYTRUDA, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).

KEYTRUDA, as a single agent, is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

KEYTRUDA is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2

or more lines of therapy.

Primary Mediastinal Large B-Cell Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy.

KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC):

- who are not eligible for any platinum-containing chemotherapy, or
- who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Non-muscle Invasive Bladder Cancer

KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

Microsatellite Instability-High or Mismatch Repair Deficient 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.

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.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal

cancer (CRC).

Gastric Cancer

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

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.

Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation either:

- in combination with platinum- and fluoropyrimidine-based chemotherapy, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.

Cervical Cancer

KEYTRUDA, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

Merkel Cell Carcinoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC). 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.

Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

KEYTRUDA, in combination with LENVIMA, is indicated for the first-line treatment of adult patients with advanced RCC.

KEYTRUDA is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

KEYTRUDA, in combination with LENVIMA, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Tumor Mutational Burden-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. 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 TMB-H central nervous system cancers have not been established.

Cutaneous Squamous Cell Carcinoma

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

Triple-Negative Breast Cancer

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test.

About LENVIMA® (lenvatinib); available as 10 mg and 4 mg capsules

LENVIMA, discovered and developed by Eisai, is a multiple receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). LENVIMA inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1-4, the platelet derived growth factor receptor alpha (PDGFR α), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2 α (FRS2 α) phosphorylation. 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. In syngeneic mouse tumor models, the combination of lenvatinib with an anti-PD-1 monoclonal antibody decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity compared to either treatment alone.

LENVIMA® (lenvatinib) Indications in the U.S.

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC)
- In combination with KEYTRUDA, for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC)
- In combination with everolimus, for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy
- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC)
- In combination with KEYTRUDA, for the treatment of patients with advanced endometrial carcinoma (EC) that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Selected Safety Information for LENVIMA

Warnings and Precautions

Hypertension. In DTC (differentiated thyroid cancer), hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC (renal cell carcinoma), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure ≥ 160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥ 100 mmHg. In HCC (hepatocellular carcinoma), hypertension occurred in 45% of LENVIMA-treated patients (24% grade 3). Grade 4 hypertension was not reported in HCC.

Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiation. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold and resume at reduced dose when hypertension is controlled or permanently discontinue based on severity.

Cardiac Dysfunction. Serious and fatal cardiac dysfunction can occur with LENVIMA. Across clinical trials in 799 patients with DTC, RCC, and HCC, grade 3 or higher cardiac dysfunction occurred in 3% of LENVIMA-treated patients. Monitor for clinical symptoms or signs of cardiac dysfunction. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Arterial Thromboembolic Events. Among patients receiving LENVIMA or LENVIMA + everolimus, arterial thromboembolic events of any severity occurred in 2% of patients in RCC and HCC and 5% in DTC. Grade 3-5 arterial thromboembolic events ranged from 2% to 3% across all clinical trials.

Among patients receiving LENVIMA with pembrolizumab, arterial thrombotic events of any severity occurred in 5% of patients in CLEAR, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

Permanently discontinue following an arterial thrombotic event. The safety of resuming 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.

Hepatotoxicity. Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. In HCC, hepatic encephalopathy occurred in 8% of LENVIMA-treated patients (5% grade 3-5). Grade 3-5 hepatic failure occurred in 3% of LENVIMA-treated patients; 2% of patients discontinued LENVIMA due to hepatic encephalopathy, and 1% discontinued due to hepatic failure.

Monitor liver function prior to initiation, then every 2 weeks for the first 2 months, and at least monthly thereafter during treatment. Monitor patients with HCC closely for signs of hepatic failure, including hepatic encephalopathy. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Renal Failure or Impairment. Serious including fatal renal failure or impairment can occur with LENVIMA. Renal impairment was reported in 14% and 7% of LENVIMA-treated patients in DTC and HCC, respectively. Grade 3-5 renal failure or impairment occurred in 3% of patients with DTC and 2% of patients with HCC, including 1 fatal event in each study. In RCC, renal impairment or renal failure was reported in 18% of LENVIMA + everolimus-treated patients (10% grade 3).

Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at reduced dose upon recovery or permanently discontinue for renal failure or impairment based on severity.

Proteinuria. In DTC and HCC, proteinuria was reported in 34% and 26% of LENVIMA-treated patients, respectively. Grade 3 proteinuria occurred in 11% and 6% in DTC and HCC, respectively. In RCC, proteinuria occurred in 31% of patients receiving LENVIMA + everolimus (8% grade 3). Monitor for proteinuria prior to initiation and periodically during treatment. If urine dipstick proteinuria $\geq 2+$ is detected, obtain a 24-hour urine protein. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Diarrhea. Of the 737 LENVIMA-treated patients in DTC and HCC, diarrhea occurred in 49% (6% grade 3). In RCC, diarrhea occurred in 81% of LENVIMA + everolimus-treated patients (19% grade 3). Diarrhea was the most frequent cause of dose interruption/reduction, and diarrhea recurred despite dose reduction. Promptly initiate management of diarrhea. Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Fistula Formation and Gastrointestinal Perforation. Of the 799 patients treated with LENVIMA or LENVIMA + everolimus in DTC, RCC, and HCC, fistula or gastrointestinal perforation occurred in 2%. Permanently discontinue in patients who develop gastrointestinal perforation of any severity or grade 3-4 fistula.

QT Interval Prolongation. In DTC, QT/QTc interval prolongation occurred in 9% of LENVIMA-treated patients and QT interval prolongation of >500 ms occurred in 2%. In RCC, QTc interval increases of >60 ms occurred in 11% of patients receiving LENVIMA + everolimus and QTc interval >500 ms occurred in 6%. In HCC, QTc interval increases of >60 ms occurred in 8% of LENVIMA-treated patients and QTc interval >500 ms occurred in 2%.

Monitor and correct electrolyte abnormalities at baseline and periodically during treatment. Monitor electrocardiograms in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Withhold and resume at reduced dose upon recovery based on severity.

Hypocalcemia. In DTC, grade 3-4 hypocalcemia occurred in 9% of LENVIMA-treated patients. In 65% of cases, hypocalcemia improved or resolved following calcium supplementation with or without dose interruption or dose reduction. In RCC, grade 3-4 hypocalcemia occurred in 6% of LENVIMA + everolimus-treated patients. In HCC, grade 3 hypocalcemia occurred in 0.8% of LENVIMA-treated patients. Monitor blood calcium levels at least monthly and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Across clinical studies of 1823 patients who received LENVIMA as a single agent, RPLS occurred in 0.3%. Confirm diagnosis of RPLS with MRI. Withhold and resume at reduced dose upon recovery or permanently discontinue depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events. Serious including fatal hemorrhagic events can occur with LENVIMA. In DTC, RCC, and HCC clinical trials, hemorrhagic events, of any grade, occurred in 29% of the 799 patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events (all grades and occurring in at least 5% of patients) were epistaxis and hematuria. In DTC, grade 3-5 hemorrhage occurred in 2% of LENVIMA-treated patients, including 1 fatal intracranial hemorrhage among 16 patients who received LENVIMA and had CNS metastases at baseline. In RCC, grade 3-5 hemorrhage occurred in 8% of LENVIMA + everolimus-treated patients, including 1 fatal cerebral hemorrhage. In HCC, grade 3-5 hemorrhage occurred in 5% of LENVIMA-treated patients, including 7 fatal hemorrhagic events. Serious tumor-related bleeds, including fatal hemorrhagic events, occurred in LENVIMA-treated patients in clinical trials and in the postmarketing setting. In postmarketing surveillance, serious and fatal carotid artery hemorrhages were seen more frequently in patients with anaplastic thyroid carcinoma (ATC) than other tumors. Safety and effectiveness of LENVIMA in patients with ATC have not been demonstrated in clinical trials.

Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (eg, carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue based on severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction. LENVIMA impairs exogenous thyroid suppression. In DTC, 88% of patients had baseline thyroid stimulating hormone (TSH) level ≤ 0.5 mU/L. In patients with normal TSH at baseline, elevation of TSH level >0.5 mU/L was observed post baseline in 57% of LENVIMA-treated patients. In RCC and HCC, grade 1 or 2 hypothyroidism occurred in 24% of LENVIMA + everolimus-treated patients and 21% of LENVIMA-treated patients, respectively. In patients with normal or low TSH at baseline, elevation of TSH was observed post baseline in 70% of LENVIMA-treated patients in HCC and 60% of

LENVIMA + everolimus-treated patients in RCC.

Monitor thyroid function prior to initiation and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing. Impaired wound healing has been reported in patients who received LENVIMA. Withhold LENVIMA for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of LENVIMA after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw (ONJ). ONJ has been reported in patients receiving LENVIMA. Concomitant exposure to other risk factors, such as bisphosphonates, denosumab, dental disease, or invasive dental procedures, may increase the risk of ONJ.

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices and to consider having preventive dentistry performed prior to treatment with LENVIMA and throughout treatment with LENVIMA.

Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

Withhold LENVIMA if ONJ develops and restart based on clinical judgement of adequate resolution.

Embryo-Fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended clinical doses resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception during treatment with LENVIMA and for at least 30 days after the last dose.

Adverse Reactions

In DTC, the most common adverse reactions ($\geq 30\%$) observed in LENVIMA-treated patients were hypertension (73%), fatigue (67%), diarrhea (67%), arthralgia/myalgia (62%), decreased appetite (54%), decreased weight (51%), nausea (47%), stomatitis (41%), headache (38%), vomiting (36%), proteinuria (34%), palmar-plantar

erythrodysesthesia syndrome (32%), abdominal pain (31%), and dysphonia (31%). The most common serious adverse reactions ($\geq 2\%$) were pneumonia (4%), hypertension (3%), and dehydration (3%). Adverse reactions led to dose reductions in 68% of LENVIMA-treated patients; 18% discontinued LENVIMA. The most common adverse reactions ($\geq 10\%$) resulting in dose reductions were hypertension (13%), proteinuria (11%), decreased appetite (10%), and diarrhea (10%); the most common adverse reactions ($\geq 1\%$) resulting in discontinuation of LENVIMA were hypertension (1%) and asthenia (1%).

In RCC, the most common adverse reactions ($\geq 20\%$) observed in LENVIMA + pembrolizumab-treated patients were fatigue (63%), diarrhea (62%), musculoskeletal pain (58%), hypothyroidism (57%), hypertension (56%), stomatitis (43%), decreased appetite (41%), rash (37%), nausea (36%), decreased weight (30%), dysphonia (30%), proteinuria (30%), palmar-plantar erythrodysesthesia syndrome (29%), abdominal pain (27%), hemorrhagic events (27%), vomiting (26%), constipation (25%), hepatotoxicity (25%), headache (23%), and acute kidney injury (21%). The most common serious adverse reactions ($\geq 2\%$) were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%). Fatal adverse reactions occurred in 4.3% of patients receiving LENVIMA in combination with pembrolizumab, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm and subarachnoid hemorrhage. Serious adverse reactions occurred in 51% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions in $\geq 2\%$ of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%). Permanent discontinuation of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 37% of patients; 26% LENVIMA only, 29% pembrolizumab only, and 13% both drugs. The most common adverse reactions ($\geq 2\%$) leading to permanent discontinuation of LENVIMA, pembrolizumab, or both were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%). Dose interruptions of LENVIMA, pembrolizumab, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA in combination with pembrolizumab. LENVIMA was interrupted in 73% of patients and both drugs were interrupted in 39% of patients. LENVIMA was dose reduced in 69% of patients. The most common adverse reactions ($\geq 5\%$) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), palmar-plantar erythrodysesthesia (11%), nausea (9%), stomatitis (9%), musculoskeletal pain (8%), rash (8%), increased lipase (7%), abdominal pain (6%), and vomiting (6%), increased ALT (5%), and increased amylase (5%).

In RCC, the most common adverse reactions ($\geq 30\%$) observed in LENVIMA + everolimus-treated patients were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension (42%), peripheral edema (42%), cough (37%), abdominal pain (37%), dyspnea (35%),

rash (35%), decreased weight (34%), hemorrhagic events (32%), and proteinuria (31%). The most common serious adverse reactions ($\geq 5\%$) were renal failure (11%), dehydration (10%), anemia (6%), thrombocytopenia (5%), diarrhea (5%), vomiting (5%), and dyspnea (5%). Adverse reactions led to dose reductions or interruption in 89% of patients. The most common adverse reactions ($\geq 5\%$) resulting in dose reductions 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 HCC, the most common adverse reactions ($\geq 20\%$) observed in LENVIMA-treated patients were hypertension (45%), fatigue (44%), diarrhea (39%), decreased appetite (34%), arthralgia/myalgia (31%), decreased weight (31%), abdominal pain (30%), palmar-plantar erythrodysesthesia syndrome (27%), proteinuria (26%), dysphonia (24%), hemorrhagic events (23%), hypothyroidism (21%), and nausea (20%). The most common serious adverse reactions ($\geq 2\%$) were hepatic encephalopathy (5%), hepatic failure (3%), ascites (3%), and decreased appetite (2%). Adverse reactions led to dose reductions or interruption in 62% of patients. The most common adverse reactions ($\geq 5\%$) resulting in dose reductions were fatigue (9%), decreased appetite (8%), diarrhea (8%), proteinuria (7%), hypertension (6%), and palmar-plantar erythrodysesthesia syndrome (5%). Treatment discontinuation due to an adverse reaction occurred in 20% of patients. The most common adverse reactions ($\geq 1\%$) resulting in discontinuation of LENVIMA were fatigue (1%), hepatic encephalopathy (2%), hyperbilirubinemia (1%), and hepatic failure (1%).

In EC, the most common adverse reactions ($\geq 20\%$) observed in LENVIMA + pembrolizumab-treated patients were hypothyroidism (67%), hypertension (67%), fatigue (58%), diarrhea (55%), musculoskeletal disorders (53%), nausea (49%), decreased appetite (44%), vomiting (37%), stomatitis (35%), decreased weight (34%), abdominal pain (34%), urinary tract infection (31%), proteinuria (29%), constipation (27%), headache (26%), hemorrhagic events (25%), palmar-plantar erythrodysesthesia (23%), dysphonia (22%), and rash (20%). Fatal adverse reactions occurred in 4.7% of those treated with LENVIMA and pembrolizumab, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction. Serious adverse reactions occurred in 50% of patients receiving LENVIMA and pembrolizumab. Serious adverse reactions with frequency $\geq 3\%$ were hypertension (4.4%), and urinary tract infection (3.2%). Discontinuation of LENVIMA due to an adverse reaction occurred in 26% of patients. The most common ($\geq 1\%$) adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), asthenia (1.8%), diarrhea (1.2%), decreased appetite (1.2%), proteinuria (1.2%), and vomiting (1.2%). Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common ($\geq 5\%$) adverse reactions resulting in dose reduction of LENVIMA were hypertension (18%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria (7%), fatigue (7%), decreased appetite (6%), asthenia (5%), and weight decreased (5%). Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of

these patients. The most common ($\geq 2\%$) adverse reactions leading to interruption of LENVIMA were hypertension (11%), diarrhea (11%), proteinuria (6%), decreased appetite (5%), vomiting (5%), increased alanine aminotransferase (3.5%), fatigue (3.5%), nausea (3.5%), abdominal pain (2.9%), weight decreased (2.6%), urinary tract infection (2.6%), increased aspartate aminotransferase (2.3%), asthenia (2.3%), and palmar-plantar erythrodysesthesia (2%).

Use in Specific Populations

Because of the potential for serious adverse reactions in breastfed infants, advise women to discontinue breastfeeding during treatment and for at least 1 week after the last dose. LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (CLcr 60-89 mL/min) or moderate (CLcr 30-59 mL/min) renal impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe (CLcr 15-29 mL/min) renal impairment. Reduce the dose for patients with DTC, RCC, or EC and severe renal impairment. There is no recommended dose for patients with HCC and severe renal impairment. LENVIMA has not been studied in patients with end-stage renal disease.

No dose adjustment is recommended for patients with HCC and mild hepatic impairment (Child-Pugh A). There is no recommended dose for patients with HCC with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is recommended for patients with DTC, RCC, or EC and mild or moderate hepatic impairment. LENVIMA concentrations may increase in patients with DTC, RCC, or EC and severe hepatic impairment. Reduce the dose for patients with DTC, RCC, or EC and severe hepatic impairment.

Please see Prescribing Information for LENVIMA (lenvatinib) at <http://www.lenvima.com/pdfs/prescribing-information.pdf>.

About the Merck and Eisai strategic collaboration

In March 2018, Eisai and Merck, known as MSD outside the United States and Canada, through an affiliate, entered into a strategic collaboration for the worldwide co-development and co-commercialization of LENVIMA. Under the agreement, the companies will jointly develop, manufacture and commercialize LENVIMA, both as monotherapy and in combination with Merck's anti-PD-1 therapy KEYTRUDA.

In addition to ongoing clinical studies evaluating the KEYTRUDA plus LENVIMA combination across several different tumor types, the companies have jointly initiated new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program and are evaluating the combination in more than 10 different tumor types across more than 15 clinical trials.

Merck's focus on cancer

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck is committed to exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck

At Merck, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of research to deliver innovative health solutions that advance the prevention and treatment of diseases in people and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe, sustainable and healthy future for all people and communities. For more information, visit www.merck.com and connect with us on [Twitter](#), [Facebook](#), [Instagram](#), [YouTube](#) and [LinkedIn](#).

Eisai's focus on cancer

Eisai focuses on the development of anticancer drugs, targeting the tumor microenvironment (with experience and knowledge from existing in-house discovered compounds) and the driver gene mutation and aberrant splicing (leveraging RNA Splicing Platform) as areas (Ricchi) where real patient needs are still unmet, and where Eisai can aim to become a frontrunner in oncology. Eisai aspires to discover innovative new drugs with new targets and mechanisms of action from these Ricchi, with the aim of contributing to the cure of cancers.

About Eisai

Eisai's Corporate Philosophy is "to give first thought to patients and people in the daily living domain, and to increase the benefits that health care provides." Under this Concept [also known as our human health care (hhc) Concept], we aim to effectively achieve social good in the form of relieving anxiety over health and reducing health disparities. With a global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to create and deliver innovative products to target diseases with high unmet medical needs, with a particular focus in

our strategic areas of Neurology and Oncology.

In addition, **our continued commitment to the elimination of neglected tropical diseases (NTDs), which is a target (3.3) of the United Nations Sustainable Development Goals (SDGs)**, is demonstrated by our work on various activities together with global partners.

For more information about Eisai, please visit **www.eisai.com** (for global headquarters: Eisai Co., Ltd.), **us.eisai.com** (for U.S. headquarters: Eisai, Inc.) or **www.eisai.eu** (for Europe, Middle East, Africa, Russia, Australia, and New Zealand headquarters: Eisai Europe Ltd.), and connect with us on Twitter (**U.S.** and **global**) and **LinkedIn** (for **U.S.** and **EMEA**).

Forward-Looking Statement of Merck & Co., Inc., Rahway, N.J., USA

This news release of Merck & Co., Inc., Rahway, 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 candidates that the candidates will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of the global outbreak of novel coronavirus disease (COVID-19); the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company’s Annual Report on Form 10-K for the year ended December 31, 2021 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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