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**FDA Approves KEYTRUDA® (pembrolizumab) plus LENVIMA® (lenvatinib)  
Combination Treatment for Patients with Certain Types of Endometrial  
Carcinoma**

**Combination Treatment Approved for Patients with Advanced Endometrial Carcinoma  
That Is Not Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR),  
Who Have Disease Progression Following Prior Systemic Therapy and Are Not  
Candidates for Curative Surgery or Radiation**

**Under New FDA-Initiated Program, Combination Treatment Is the First to Receive  
Simultaneous Review Decisions in the U.S., Australia and Canada**

KENILWORTH, N.J., and WOODCLIFF LAKE, N.J., Sept. 17, 2019 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, and Eisai today announced that the U.S. Food and Drug Administration (FDA) approved the combination of KEYTRUDA, Merck's anti-PD-1 therapy, plus LENVIMA, the orally available kinase inhibitor discovered by Eisai, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This marks the first U.S. approval for the combination of KEYTRUDA plus LENVIMA and the first time an anti-PD-1 therapy is approved in combination with a kinase inhibitor for advanced endometrial carcinoma in the U.S. Following submission on June 17, this is an accelerated approval reviewed under the FDA's Real-Time Oncology Review (RTOR) pilot program, which aims to improve the efficiency of the review process for applications to ensure that treatments are available to patients as early as possible. This approval is 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 trial. According to the FDA, this review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among its international partners. Under this project, the FDA, the Australian Therapeutic Goods

Administration (TGA) and Health Canada collaboratively reviewed applications for two oncology drugs, allowing for simultaneous decisions in all three countries.

“When diagnosed early, endometrial carcinoma can have a good prognosis; however, for women whose cancer has progressed following prior systemic therapy, there are few FDA-approved treatment options,” said Dr. Vicky Makker, medical oncologist, Memorial Sloan Kettering Cancer Center. “Based on objective response rate and the duration of response, this approval of the KEYTRUDA plus LENVIMA combination will help address a significant unmet medical need for patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.”

Immune-mediated adverse reactions, which may be severe or fatal, can occur with KEYTRUDA, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, severe skin reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation (HSCT). Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered if appropriate. KEYTRUDA can also cause severe or life-threatening infusion-related reactions. Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. For more information, see “Selected Important Safety Information” below.

Adverse reactions, some of which can be serious or fatal, may occur with LENVIMA, including hypertension, cardiac dysfunction, arterial thromboembolic events, hepatotoxicity, renal failure or impairment, proteinuria, diarrhea, fistula formation and gastrointestinal perforation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impairment of thyroid stimulating hormone suppression/thyroid dysfunction, and wound healing complications. Based on the type and/or severity of the adverse reaction, LENVIMA may be interrupted, reduced and/or discontinued. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to use effective contraception. For more information, see “Selected Safety Information” below.

“Today’s approval of the KEYTRUDA plus LENVIMA combination for advanced endometrial carcinoma that has progressed following prior systemic therapy brings the first approved combination treatment to women with this type of cancer whose tumors are not MSI-H or dMMR and who are not candidates for curative surgery or radiation, and demonstrates the potential of our collaboration with Eisai,” said Dr. Jonathan Cheng, Vice President, Oncology Clinical Research, Merck Research Laboratories. “Merck is committed to developing this

combination through the LEAP (LEnvatinib And Pembrolizumab) clinical program, which is under active investigation.”

“At least 75% of endometrial cancer cases are not microsatellite instability-high or mismatch repair deficient, and these women have been in need of new treatment options,” said Dr. Takashi Owa, Vice President, Chief Medicine Creation and Chief Discovery Officer, Oncology Business Group at Eisai. “We are excited for the advancement that today’s approval of the KEYTRUDA plus LENVIMA combination treatment represents for these women whose advanced endometrial carcinoma is not microsatellite instability-high or mismatch repair deficient, has progressed following prior systemic therapy and who are not candidates for curative surgery or radiation, and we look forward to the possibilities that our collaboration holds.”

### **Data Supporting the Approval**

The approval was based on data from KEYNOTE-146/Study 111, a Phase 2, multi-cohort, multicenter, open-label, single-arm trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were treated with KEYTRUDA 200 mg intravenously every three weeks in combination with LENVIMA 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator.

Administration of KEYTRUDA plus LENVIMA was permitted beyond Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA dosing was continued for a maximum of 24 months; however, treatment with LENVIMA could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every six weeks until week 24, followed by every nine weeks thereafter. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) by independent radiologic review committee (IRC) using RECIST 1.1.

Among the 108 patients, 87% (n=94) had tumors that were not MSI-H or dMMR, 10% (n=11) had tumors that were MSI-H or dMMR, and 3% (n=3) had tumors that had unknown status. The baseline characteristics of the 94 patients with tumors that were not MSI-H or dMMR were: median age of 66 years, with 62% age 65 or older; 86% White, 6% Black, 4% Asian, and 3% other races; and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of

0 (52%) or 1 (48%). All 94 patients had received prior systemic therapy for endometrial carcinoma; 51% had one, 38% had two, and 11% had three or more prior systemic therapies.

In the 94 patients with tumors that were not MSI-H or dMMR, the KEYTRUDA plus LENVIMA combination demonstrated an ORR of 38.3% (95% CI, 29%-49%), with a complete response rate of 10.6% (n=10) and a partial response rate of 27.7% (n=26). The median follow-up time was 18.7 months. In the patients who had a response as determined by independent review (n=36), at the time of data cutoff, the median DOR was not reached (range: 1.2+ to 33.1+ months), and 69% of these patients experienced responses lasting six months or greater.

The median duration of study treatment was seven months (range: 0.03 to 37.8 months), and the median duration of exposure to KEYTRUDA was six months (range: 0.03 to 23.8 months). Fatal adverse reactions occurred in 3% of patients treated with KEYTRUDA plus LENVIMA, including gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS) with intraventricular hemorrhage, and intracranial hemorrhage. Serious adverse reactions occurred in 52% of patients receiving KEYTRUDA plus LENVIMA. The most common serious adverse reactions ( $\geq 3\%$ ) with the KEYTRUDA plus LENVIMA combination were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage, fatigue, nausea, confusional state, and pleural effusion (4% each), adrenal insufficiency, colitis, dyspnea, and pyrexia (3% each).

KEYTRUDA was discontinued due to adverse reactions (Grade 1-4) in 19% of patients, regardless of action taken with LENVIMA. The most common adverse reactions ( $\geq 2\%$ ) leading to discontinuation of KEYTRUDA were adrenal insufficiency, colitis, pancreatitis, and muscular weakness (2% each). Permanent discontinuation due to adverse reactions (Grade 1-4) occurred in 21% of patients who received KEYTRUDA plus LENVIMA. The most common adverse reactions ( $\geq 2\%$ ) resulting in discontinuation of LENVIMA were gastrointestinal perforation or fistula, muscular weakness, and pancreatitis (2% each).

Adverse reactions leading to interruption of KEYTRUDA occurred in 49% of patients. The most common adverse reactions leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were fatigue (14%), diarrhea and decreased appetite (6% each), rash (5%), renal impairment, vomiting, increased lipase, and decreased weight (4% each), nausea, increased blood alkaline phosphatase, and skin ulcer (3% each), adrenal insufficiency, increased amylase, hypocalcemia, hypomagnesemia, hyponatremia, peripheral edema, musculoskeletal pain, pancreatitis, and syncope (2% each). Adverse reactions led to dose reduction or interruption in 88% of patients receiving LENVIMA. The most common adverse reactions ( $\geq 5\%$ ) resulting in dose reduction or interruption of LENVIMA were fatigue (32%), hypertension (26%), diarrhea

(18%), nausea, palmar-plantar erythrodysesthesia, and vomiting (13% each), decreased appetite (12%), musculoskeletal pain (11%), stomatitis (9%), abdominal pain, hemorrhages (7% each), renal impairment and decreased weight (6% each), rash, headache, increased lipase, and proteinuria (5% each).

The most common adverse reactions ( $\geq 20\%$ ) with the KEYTRUDA plus LENVIMA combination were fatigue, musculoskeletal pain, and hypertension (65% each), diarrhea (64%), decreased appetite (52%), hypothyroidism (51%), nausea (48%), stomatitis (43%), vomiting (39%), decreased weight (36%), abdominal pain and headache (33% each), constipation (32%), urinary tract infection (31%), dysphonia (29%), hemorrhagic events (28%), hypomagnesemia (27%), palmar-plantar erythrodysesthesia syndrome (26%), dyspnea (24%), cough and rash (21% each).

### **Recommended Dosage for Endometrial Carcinoma**

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every three weeks in combination with LENVIMA 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression. Refer to the LENVIMA prescribing information for recommended dosing information, as appropriate.

### **About KEYTRUDA<sup>®</sup> (pembrolizumab) Injection, 100 mg**

KEYTRUDA is an anti-PD-1 therapy that works by increasing the ability of the body's immune system to help detect and fight tumor cells. KEYTRUDA is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes which may affect both tumor cells and healthy cells.

Merck has the industry's largest immuno-oncology clinical research program. There are currently more than 1,000 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.

### **KEYTRUDA<sup>®</sup> (pembrolizumab) Indications**

#### *Melanoma*

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

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) 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.

#### *Small Cell Lung Cancer*

KEYTRUDA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of 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 confirmatory trials.

#### *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)  $\geq 1$ ] as determined by an FDA-approved test.

KEYTRUDA, as a single agent, 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.

#### *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 3 or more prior lines of 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.

#### *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. 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 confirmatory trials. 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 cisplatin-containing chemotherapy and whose tumors express PD-L1 [combined positive score (CPS)  $\geq 10$ ] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. 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 confirmatory trials.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

#### *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.

#### *Gastric Cancer*

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 (CPS  $\geq 1$ ) 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.

#### *Esophageal Cancer*

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS  $\geq 10$ ) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

#### *Cervical Cancer*

KEYTRUDA 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  $\geq 1$ ) as determined by an FDA-approved test. 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.

#### *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.

#### *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 patients with advanced renal cell carcinoma (RCC).

#### *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 and are not candidates for curative surgery or radiation. 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.

### **Selected Important Safety Information for KEYTRUDA**

#### **Immune-Mediated Pneumonitis**

KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 3.4% (94/2799) of patients with various cancers receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%).

Pneumonitis occurred in 8.2% (65/790) of NSCLC patients receiving KEYTRUDA as a single agent, including Grades 3-4 in 3.2% of patients, and occurred more frequently in patients with a history of prior thoracic radiation (17%) compared to those without (7.7%). Pneumonitis occurred in 6% (18/300) of HNSCC patients receiving KEYTRUDA as a single agent, including Grades 3-5 in 1.6% of patients, and occurred in 5.4% (15/276) of patients receiving KEYTRUDA in combination with platinum and FU as first-line therapy for advanced disease, including Grades 3-5 in 1.5% of patients.

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.

### **Immune-Mediated Colitis**

KEYTRUDA can cause immune-mediated colitis. Colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 2 (0.4%), 3 (1.1%), and 4 (<0.1%). 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.

### **Immune-Mediated Hepatitis (KEYTRUDA) and Hepatotoxicity (KEYTRUDA in Combination With Axitinib)**

#### *Immune-Mediated Hepatitis*

KEYTRUDA can cause immune-mediated hepatitis. Hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%). 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.

#### *Hepatotoxicity in Combination With Axitinib*

KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes 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.

### **Immune-Mediated Endocrinopathies**

KEYTRUDA can cause hypophysitis, thyroid disorders, and type 1 diabetes mellitus. Hypophysitis occurred in 0.6% (17/2799) of patients, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%). Hypothyroidism occurred in 8.5% (237/2799) of patients, including Grade 2 (6.2%) and 3 (0.1%). The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC (16%) receiving KEYTRUDA, as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. Hyperthyroidism occurred in 3.4% (96/2799) of patients, including Grade 2 (0.8%) and 3 (0.1%), and thyroiditis occurred in 0.6% (16/2799) of patients, including Grade 2 (0.3%). Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 0.2% (6/2799) of patients.

Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency), thyroid function (prior to and periodically during treatment), and hyperglycemia. For hypophysitis, administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2 and withhold or discontinue for Grade 3 or 4 hypophysitis. Administer hormone replacement for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for Grade 3 or 4 hyperthyroidism. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer antihyperglycemics in patients with severe hyperglycemia.

### **Immune-Mediated Nephritis and Renal Dysfunction**

KEYTRUDA can cause immune-mediated nephritis. Nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.1%), and 4 (<0.1%) nephritis. Nephritis occurred in 1.7% (7/405) of patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy. Monitor patients for changes in renal function. Administer corticosteroids for Grade 2 or greater nephritis. Withhold KEYTRUDA for Grade 2; permanently discontinue for Grade 3 or 4 nephritis.

### **Immune-Mediated Skin Reactions**

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.

### **Other Immune-Mediated Adverse Reactions**

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving KEYTRUDA and may also occur after discontinuation of treatment. 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, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including classical Hodgkin lymphoma, and postmarketing use.

Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment vs the risk of possible organ rejection in these patients.

### **Infusion-Related Reactions**

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% (6/2799) of patients. Monitor patients for signs and symptoms of infusion-related reactions. For Grade 3 or 4 reactions, stop infusion and permanently discontinue KEYTRUDA.

### **Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic HSCT after treatment with KEYTRUDA. Of 23 patients with cHL who proceeded to allogeneic HSCT after KEYTRUDA, 6 (26%) developed graft-versus-host disease (GVHD) (1 fatal case) and 2 (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning (1 fatal case). 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. Follow patients closely for early evidence of transplant-related complications such as hyperacute graft-versus-host disease (GVHD), Grade 3 to 4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions.

In patients with a history of allogeneic HSCT, acute GVHD (including fatal GVHD) has been reported after treatment with KEYTRUDA. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after KEYTRUDA. Consider the benefit of KEYTRUDA vs the risk of GVHD in these patients.

### **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 a PD-1 or PD-L1 blocking antibody 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-002, KEYTRUDA was permanently discontinued due to adverse reactions in 12% of 357 patients with advanced melanoma; the most common ( $\geq 1\%$ ) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). The most common adverse reactions were fatigue (43%), pruritus (28%), rash (24%), constipation (22%), nausea (22%), diarrhea (20%), and decreased appetite (20%).

In KEYNOTE-054, 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-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; 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%).

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

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-087, KEYTRUDA was discontinued due to adverse reactions in 5% of 210 patients with cHL. Serious adverse reactions occurred in 16% of patients; those  $\geq 1\%$  included 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 metastatic urothelial carcinoma. 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 metastatic urothelial carcinoma. 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%).

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

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

In KEYNOTE-158, KEYTRUDA was discontinued due to adverse reactions in 8% of 98 patients with 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 hepatocellular carcinoma (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-146, when KEYTRUDA was administered in combination with lenvatinib to patients with endometrial carcinoma (n=94), fatal adverse reactions occurred in 3% of patients. Serious adverse reactions occurred in 52% of patients, the most common ( $\geq 3\%$ ) were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage, fatigue, nausea, confusional state, and pleural effusion (4% each), adrenal insufficiency, colitis, dyspnea, and pyrexia (3% each).

KEYTRUDA was discontinued for adverse reactions (Grade 1-4) in 19% of patients, regardless of action taken with lenvatinib; the most common ( $\geq 2\%$ ) leading to discontinuation of KEYTRUDA were adrenal insufficiency, colitis, pancreatitis, and muscular weakness (2% each).

The most common adverse reactions ( $\geq 20\%$ ) observed with KEYTRUDA in combination with LENVIMA were fatigue, musculoskeletal pain and hypertension (65% each), diarrhea (64%), decreased appetite (52%), hypothyroidism (51%), nausea (48%), stomatitis (43%), vomiting (39%), decreased weight (36%), abdominal pain and headache (33% each), constipation (32%), urinary tract infection (31%), dysphonia (29%), hemorrhagic events (28%), hypomagnesaemia (27%), palmar-plantar erythrodysesthesia syndrome (26%), dyspnea (24%), cough and rash (21% each).

## 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

There is limited experience in pediatric patients. In a trial, 40 pediatric patients (16 children aged 2 years to younger than 12 years and 24 adolescents aged 12 years to 18 years) with various cancers, including unapproved usages, 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 2 doses or more. The safety profile in these pediatric patients was similar to that seen in adults; adverse reactions that occurred at a higher rate ( $\geq 15\%$  difference) in these patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), increased transaminases (28%), and hyponatremia (18%).

**Please see Prescribing Information for KEYTRUDA (pembrolizumab) at**

**[http://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf) and**

**Medication Guide for KEYTRUDA at**

**[http://www.merck.com/product/usa/pi\\_circulars/k/keytruda/keytruda\\_mg.pdf](http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_mg.pdf).**

## About LENVIMA® (lenvatinib) Capsules, 10 mg and 4 mg

LENVIMA® (lenvatinib) is a kinase inhibitor that is indicated:

- For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (RAI-refractory DTC)
- In combination with everolimus for the treatment of 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 that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy, and are not candidates for curative surgery or radiation. 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 trial

LENVIMA, discovered and developed by Eisai, is a 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 $\alpha$ ), KIT, and RET. In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.

## **Selected Safety Information**

### **Warnings and Precautions**

**Hypertension.** In DTC, hypertension occurred in 73% of patients on LENVIMA (44% grade 3-4). In RCC, hypertension occurred in 42% of patients on LENVIMA + everolimus (13% grade 3). Systolic blood pressure  $\geq$ 160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure  $\geq$ 100 mmHg. In HCC, 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. 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 1,327 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.** Across clinical studies of 1,823 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  $\leq 0.5$  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.

**Wound Healing Complications.** Wound healing complications, including fistula formation and wound dehiscence, can occur with LENVIMA. Withhold for at least 6 days prior to scheduled surgery. Resume after surgery based on clinical judgment of adequate wound healing. Permanently discontinue in patients with wound healing complications.

**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

(≥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 (≥10%) resulting in dose reductions 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 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 (≥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 (≥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 (≥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 (≥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 (≥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 (≥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 (≥20%) observed in LENVIMA + pembrolizumab - treated patients were fatigue (65%), hypertension (65%), musculoskeletal pain (65%), diarrhea (64%), decreased appetite (52%), hypothyroidism (51%), nausea (48%), stomatitis (43%), vomiting (39%), decreased weight (36%), abdominal pain (33%), headache

(33%), constipation (32%), urinary tract infection (31%), dysphonia (29%), hemorrhagic events (28%), hypomagnesemia (27%), palmar-plantar erythrodysesthesia (26%), dyspnea (24%), cough (21%) and rash (21%).

Adverse reactions led to dose reduction or interruption in 88% of patients receiving LENVIMA. The most common adverse reactions ( $\geq 5\%$ ) resulting in dose reduction or interruption of LENVIMA were fatigue (32%), hypertension (26%), diarrhea (18%), nausea (13%), palmar-plantar erythrodysesthesia (13%), vomiting (13%), decreased appetite (12%), musculoskeletal pain (11%), stomatitis (9%), abdominal pain (7%), hemorrhages (7%), renal impairment (6%), decreased weight (6%), rash (5%), headache (5%), increased lipase (5%) and proteinuria (5%).

Fatal adverse reactions occurred in 3% of patients receiving LENVIMA + pembrolizumab, including gastrointestinal perforation, RPLS with intraventricular hemorrhage, and intracranial hemorrhage.

Serious adverse reactions occurred in 52% of patients receiving LENVIMA + pembrolizumab. Serious adverse reactions in  $\geq 3\%$  of patients were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage (4%), fatigue (4%), nausea (4%), confusional state (4%), pleural effusion (4%), adrenal insufficiency (3%), colitis (3%), dyspnea (3%), and pyrexia (3%).

Permanent discontinuation due to adverse reaction (Grade 1-4) occurred in 21% of patients who received LENVIMA + pembrolizumab. The most common adverse reactions ( $\geq 2\%$ ) resulting in discontinuation of LENVIMA were gastrointestinal perforation or fistula (2%), muscular weakness (2%), and pancreatitis (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 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 Eisai and Merck 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 will jointly initiate new clinical studies through the LEAP (LEnvatinib And Pembrolizumab) clinical program, which will evaluate the combination to support 11 potential indications in six types of cancer. The LEAP clinical program also includes a new basket trial targeting six additional cancer types.

### **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](http://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. For more information, visit [www.merck.com](http://www.merck.com) and connect with us on [Twitter](#), [Facebook](#), [Instagram](#), [YouTube](#) and [LinkedIn](#).

### **About Eisai**

Eisai is a leading global research and development-based pharmaceutical company headquartered in Japan, with approximately 10,000 employees worldwide. 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. We strive to realize our *hhc* philosophy by delivering innovative products in therapeutic areas with high unmet medical needs, including Oncology and Neurology. In the spirit of *hhc*, we take that commitment even further by applying our scientific expertise, clinical capabilities and patient insights to discover and develop innovative solutions that help address society’s toughest unmet needs, including neglected tropical diseases and the Sustainable Development Goals.

For more information about Eisai, please visit [www.eisai.com](http://www.eisai.com) (for global), [us.eisai.com](http://us.eisai.com) (for U.S.) or [www.eisai.co.uk](http://www.eisai.co.uk) (for U.K.), and connect with us on Twitter ([U.S.](#) and [global](#)) and [LinkedIn](#) (for U.S.).

### **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 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 2018 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 (<http://www.sec.gov>).

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