



NEWS RELEASE

# KEYTRUDA® (pembrolizumab) Plus LENVIMA® (lenvatinib) Combination Demonstrated Statistically Significant Improvement in Overall Survival, Progression-Free Survival and Objective Response Rate Versus Chemotherapy in Patients With Advanced...

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First Overall Survival Analysis for KEYTRUDA Plus LENVIMA Combination in a Phase 3 Study in Advanced Endometrial Cancer

KENILWORTH, N.J. & WOODCLIFF LAKE, N.J.--(BUSINESS WIRE)--

**KEYTRUDA® (pembrolizumab) Plus LENVIMA® (lenvatinib) Combination Demonstrated Statistically Significant Improvement in Overall Survival, Progression-Free Survival and Objective Response Rate Versus Chemotherapy in Patients With Advanced Endometrial Cancer Following Prior Systemic Therapy in Phase 3 Study**

Merck (NYSE: MRK), known as MSD outside the United States and Canada, and Eisai today announced that the pivotal Phase 3 KEYNOTE-775/Study 309 trial evaluating the investigational use of KEYTRUDA, Merck's anti-PD-1 therapy, plus LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, met its dual primary endpoints of overall survival (OS) and progression-free survival (PFS) and its secondary efficacy endpoint of objective response rate (ORR) in patients with advanced endometrial cancer following at least one prior platinum-based regimen. These positive results were observed in the mismatch repair proficient (pMMR) subgroup

and the intention-to-treat (ITT) study population, which includes both patients with endometrial carcinoma that is pMMR as well as patients whose disease is microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR). Based on an analysis conducted by an independent Data Monitoring Committee, KEYTRUDA plus LENVIMA demonstrated a statistically significant and clinically meaningful improvement in OS, PFS and ORR versus chemotherapy (treatment of physician's choice [TPC] of doxorubicin or paclitaxel). The safety profile of the KEYTRUDA plus LENVIMA combination was consistent with previously reported studies. Merck and Eisai will discuss these data with regulatory authorities worldwide, with the intent to submit marketing authorization applications based on these results, and plan to present these results at an upcoming medical meeting.

"Women with advanced endometrial cancer are faced with high mortality rates and limited treatment options following initial systemic therapy," said Dr. Gregory Lubiniecki, Associate Vice President, Oncology Clinical Research, Merck Research Laboratories. "These are the first results from a Phase 3 trial of a combination regimen including immunotherapy in advanced endometrial carcinoma that have shown a statistically significant improvement in overall survival, progression-free survival and objective response rate versus chemotherapy. Merck and Eisai are dedicated to continuing to research the KEYTRUDA plus LENVIMA combination and discover new approaches to address unmet needs for devastating diseases such as endometrial carcinoma."

"We are encouraged by the data observed in KEYNOTE-775/Study 309, which represent a possible step forward for patients impacted by advanced endometrial carcinoma and support the results seen in the advanced endometrial cancer cohort of KEYNOTE-146/Study 111," said Dr. Takashi Owa, Vice President, Chief Medicine Creation Officer and Chief Discovery Officer, Oncology Business Group at Eisai. "As more clinical data from the LEAP (LEnvatinib And Pembrolizumab) program are revealed, we cannot help but be energized by the trajectory of our collaboration with Merck and the benefits we hope to provide to patients together. Most importantly, we are grateful for the trust that the patients and healthcare professionals who participated in this trial have shown us."

KEYNOTE-775/Study 309 is the confirmatory trial for KEYNOTE-146/Study 111, which supported the U.S. Food and Drug Administration's (FDA) 2019 accelerated approval of the KEYTRUDA plus LENVIMA combination 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 accelerated approval was based on tumor response rate and durability of response and was the first approval granted under Project Orbis, an initiative of the FDA Oncology Center of Excellence that provides a framework for concurrent submission and review of oncology drugs among its international partners. Under Project Orbis, Health Canada and Australia's Therapeutic Goods Administration (TGA) granted conditional and provisional approvals, respectively, for this indication.

Merck and Eisai are studying the KEYTRUDA plus LENVIMA combination through the LEAP (LEnvatinib And

Pembrolizumab) clinical program in 13 different tumor types across 20 clinical trials, including a Phase 3 trial evaluating the combination in the first-line setting for patients with advanced endometrial carcinoma (LEAP-001).

## About KEYNOTE-775/Study 309

KEYNOTE-775/Study 309 is a multicenter, randomized, open-label, Phase 3 trial ([ClinicalTrials.gov, NCT03517449](https://clinicaltrials.gov/ct2/show/study/NCT03517449)) evaluating KEYTRUDA in combination with LENVIMA in patients with advanced endometrial cancer following at least one prior platinum-based regimen. The dual primary endpoints are OS and PFS, as assessed by Blinded Independent Central Review (BICR) per Response Evaluation Criteria in Solid Tumors Version (RECIST) v1.1. Select secondary endpoints include objective response rate (ORR) by BICR per RECIST v1.1 and safety/tolerability. Of the 827 patients enrolled, 697 patients had tumors that were non-MSI-H or pMMR, and 130 patients had tumors that were MSI-H or dMMR. Patients were randomized 1:1 to receive:

- KEYTRUDA (200 mg intravenously [IV] every three weeks) for up to 35 cycles (approximately two years) in combination with LENVIMA (20 mg orally once daily); or
- Chemotherapy (Treatment of physician's choice [TPC] of either doxorubicin 60 mg/m<sup>2</sup> IV every three weeks for up to a maximum cumulative dose of 500 mg/m<sup>2</sup> or paclitaxel 80 mg/m<sup>2</sup> IV on a 28-day cycle [three weeks of receiving weekly paclitaxel and one week of not receiving paclitaxel])

## About Endometrial Cancer

Endometrial cancer begins in the inner lining of the uterus, which is known as the endometrium and is the most common type of cancer in the uterus. In 2018, it was estimated there were more than 382,000 new cases and nearly 90,000 deaths from uterine body cancers worldwide (these estimates include both endometrial cancers and uterine sarcomas; more than 90% of uterine body cancers occur in the endometrium, so the actual numbers for endometrial cancer cases and deaths are slightly lower than these estimates). In the U.S., it is estimated there will be almost 66,000 new cases of uterine body cancer and nearly 13,000 deaths from the disease in 2020. The five-year survival rate for advanced or metastatic endometrial cancer (stage IV) is estimated to be approximately 17%.

About KEYTRUDA® (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 1,300 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.

### 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 1 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 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 cisplatin-containing chemotherapy and whose tumors express PD-L1 (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.

KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) 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, 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.

#### Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

#### 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 trial.

#### Tumor Mutational Burden-High

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [ $\geq 10$  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) that is not curable by surgery or radiation.

### Triple-Negative Breast Cancer

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (CPS  $\geq 10$ ) as determined by an FDA-approved test. This indication is approved under accelerated approval based on progression-free survival. 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

### Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or the programmed death ligand 1 (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.

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. 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, 42% of these patients 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 as a Single Agent

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, which was at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT  $\geq 3$  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  $\geq 3$  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  $\geq 3$  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). 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 treatment. 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, 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 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%).

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-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 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%).

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.

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 LENVIMA 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 LENVIMA; 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%), hypomagnesemia (27%), palmar-plantar erythrodysesthesia syndrome (26%), dyspnea (24%), and cough and rash (21% each).

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 cSCC were similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a monotherapy.

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 (n=596) who had not been previously treated with chemotherapy in the metastatic setting, 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 most common were: pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%). KEYTRUDA was discontinued in 11% of patients due to adverse reactions. The most common adverse 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%).

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

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 discontinued 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 (e.g., 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.

**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.

**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 ( $\geq 30\%$ ) 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 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 ( $>2\%$ ) 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.

LENVIMA (lenvatinib) is available as 10 mg and 4 mg capsules.

**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 13 different tumor types (endometrial carcinoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial cancer, biliary tract cancer, colorectal cancer, gastric cancer, glioblastoma, ovarian cancer and triple-negative breast cancer) across 20 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](http://www.merck.com/clinicaltrials).

## About Merck

For more than 125 years, Merck, 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 in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit [www.merck.com](http://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 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.eu](http://www.eisai.eu) (for Europe, Middle East, Africa), 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 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 2019 Annual Report on Form 10-

K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site ([www.sec.gov](http://www.sec.gov)).

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