



NEWS RELEASE

U.S. FDA Approves WELIREG® (belzutifan) Plus LENVIMA® (lenvatinib) for Certain Previously Treated Adult Patients With Advanced Renal Cell Carcinoma With a Clear Cell Component (ccRCC)

2026-09-25

Approval based on results from the Phase 3 LITESPARK-011 trial evaluating WELIREG in combination with LENVIMA compared to cabozantinib for the treatment of patients with advanced ccRCC following treatment with a PD-1/PD-L1 inhibitor

WELIREG plus LENVIMA is the first approved combination of a HIF-2 alpha inhibitor and a multi-targeted VEGFR-TKI for these patients

RAHWAY, N.J. & NUTLEY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, and Eisai today announced the U.S. Food and Drug Administration (FDA) has approved the dual oral regimen of WELIREG® (belzutifan), Merck's first-in-class oral hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor, plus LENVIMA® (lenvatinib), the orally available multiple receptor tyrosine kinase inhibitor (TKI) discovered by Eisai, for the treatment of adult patients with advanced renal cell carcinoma with a clear cell component (ccRCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

The approval is based on data from the Phase 3 LITESPARK-011 trial. Results from a pre-specified interim analysis showed treatment with WELIREG plus LENVIMA led to a statistically significant and clinically meaningful improvement in progression-free survival (PFS), one of the dual primary endpoints, compared to cabozantinib, reducing the risk of disease progression or death by 26% (HR=0.74 [95% CI, 0.61-0.89]; p=0.001) in patients with advanced ccRCC following a PD-1 or PD-L1 inhibitor. WELIREG plus LENVIMA resulted in a median PFS of 14.6

months (95% CI, 11.1-16.6) versus 10.6 months (95% CI, 9.2-11.1) with cabozantinib. WELIREG plus LENVIMA also demonstrated a statistically significant improvement in objective response rate (ORR), a key secondary endpoint, with an ORR of 53% (95% CI, 47-58) versus 40% (95% CI, 35-45) for cabozantinib ($p=0.0002$). Data for duration of response (DOR), another secondary endpoint, were also reported. At the final analysis, overall survival (OS), the study's other primary endpoint, did not meet statistical significance for patients who received WELIREG plus LENVIMA versus cabozantinib. These results will be presented at the upcoming European Society for Medical Oncology (ESMO) Congress 2026 in Madrid, Spain.

The WELIREG prescribing information contains a boxed warning that exposure to WELIREG during pregnancy can cause embryo-fetal harm. Verify pregnancy status prior to the initiation of WELIREG. Advise patients of these risks and the need for effective non-hormonal contraception. WELIREG can render some hormonal contraceptives ineffective. WELIREG can cause severe anemia that can require a blood transfusion. Monitor for anemia before initiation of and periodically throughout treatment with WELIREG. WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen or hospitalization. Monitor oxygen saturation before initiation of and periodically throughout treatment with WELIREG. Serious cardiac dysfunction, including heart failure with reduced left ventricular ejection fraction (LVEF), and cardiomyopathy, can occur with WELIREG in combination with LENVIMA. The safety of WELIREG in combination with LENVIMA has not been established in patients with LVEF below 50%. Monitor patients for symptoms or signs of heart failure and if present, reassess LVEF. Withhold and resume at a reduced dose upon recovery to baseline or Grade 1 or permanently discontinue WELIREG in combination with LENVIMA based on severity. For more information, see "Selected 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, QTc interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impairment of thyroid stimulating hormone suppression/thyroid dysfunction, impaired wound healing, osteonecrosis of the jaw and embryo-fetal toxicity. 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, and based on the severity of the adverse reaction, LENVIMA should be interrupted, reduced and/or discontinued. For more information, see "Selected Safety Information" below.

"While there has been much progress in the first-line treatment of advanced kidney cancer, we have limited options to offer patients if the disease progresses after treatment with a PD-1/PD-L1 immunotherapy," said Dr. Robert Motzer, Principal Investigator and Genitourinary Medical Oncologist, Memorial Sloan Kettering Cancer Center. "With this FDA approval of belzutifan plus lenvatinib, we have a new treatment option for patients who progress following treatment with anti-PD-1/PD-L1 therapy – an important development for patients and the physicians who care for

them.”

“By bringing together two therapies that each target different pathways, WELIREG plus LENVIMA is now the first approved regimen of its kind, offering a new treatment option for certain patients with advanced renal cell carcinoma who have progressed after anti-PD-1/PD-L1 therapy,” said Dr. M. Catherine Pietanza, Vice President, Global Clinical Development, Merck Research Laboratories. “This approval represents real progress for patients and further reinforces the importance of a HIF-2 α inhibitor plus TKI combination as a new treatment approach for these patients.”

“Patients facing advanced renal cell carcinoma need treatment options at every stage of their journey, and the complexity of managing this disease over time makes every treatment decision meaningful,” said Dr. Corina Dutcus, Senior Vice President, Oncology Global Clinical Development Lead at Eisai. “Combination approaches with LENVIMA have shaped the treatment landscape for advanced RCC from frontline therapy through later lines, and this FDA approval builds on that legacy by introducing WELIREG plus LENVIMA – the first and only approved combination following a PD-1/PD-L1 inhibitor. At Eisai, our science is driven by the humanity of the patients we serve, and, alongside Merck, we are proud to continue advancing combination treatment options with LENVIMA for the kidney cancer community.”

LENVIMA is approved in the U.S., European Union (EU), Japan, and other regions in combination with multiple agents for the treatment of RCC. In the U.S., it is approved for the following indications:

- LENVIMA, in combination with KEYTRUDA ®(pembrolizumab) or KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph), is approved for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
- LENVIMA, in combination with everolimus, is approved for the treatment of adult patients with advanced RCC following one prior anti-angiogenic therapy.

Lenvatinib is approved as KISPLYX for advanced RCC in the EU.

WELIREG is approved in the U.S., EU, Japan, and other regions as a monotherapy and in combination treatment options for the treatment of RCC. In the U.S., it is approved for the following indications:

- WELIREG, as monotherapy, is approved for the treatment of adult patients with advanced ccRCC following a PD-1 or PD-L1 inhibitor and a VEGF-TKI.
- WELIREG, in combination with KEYTRUDA or KEYTRUDA QLEX, is approved for the adjuvant treatment of adult patients with ccRCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Dr. Motzer has provided consulting and advisory services for Merck and Eisai.

Study design and additional data from LITESPARK-011

LITESPARK-011 is a randomized, open-label Phase 3 trial (ClinicalTrials.gov, **NCT04586231**) evaluating WELIREG in combination with LENVIMA compared to cabozantinib for the treatment of patients with advanced ccRCC. Eligible patients include participants with locally advanced or metastatic ccRCC who have progressed on or after a PD-1 or PD-L1 inhibitor, or within 6 months of completing adjuvant therapy with a PD-1 inhibitor. The study excluded patients with hypoxia, active CNS metastases and clinically significant cardiac disease within 6 months before first dose of study intervention. The trial enrolled 747 patients who were randomized to receive WELIREG (120 mg orally once daily) plus LENVIMA (20 mg orally once daily) or cabozantinib (60 mg orally once daily). The major efficacy endpoints were PFS per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as assessed by blinded independent central review (BICR) and OS. Additional efficacy endpoints included ORR by BICR using RECIST v1.1.

The median duration of exposure to WELIREG was 15.8 months (range: 1 day to 50.6 months) and the median duration of exposure to LENVIMA was 14.5 months (range: 1 day to 50.6 months).

Serious adverse reactions occurred in 54% of patients treated with WELIREG in combination with LENVIMA. Serious adverse reactions in $\geq 2\%$ of patients included hypoxia (6%), pneumonia (5%), hyponatremia (3.2%), acute kidney injury (3%), hemorrhage (2.7%), anemia (2.7%), cardiac failure (2.4%) and diarrhea (2.4%).

Fatal adverse reactions occurred in 5% of patients who received WELIREG in combination with LENVIMA, including sepsis (0.8%), pneumonia (0.5%), pneumonitis (0.5%), respiratory failure (0.5%) and one case (0.3%) each of acute cholecystitis, acute respiratory distress syndrome, pulmonary edema, embolic cerebral infarction, hemorrhage, postoperative wound complication, thrombotic microangiopathy and upper respiratory tract infection.

Permanent discontinuation of WELIREG due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of WELIREG in $>0.5\%$ of patients included hypoxia (2.2%), pneumonia (1.1%), fatigue (0.8%), hyponatremia (0.8%), pneumonitis (0.8%) and respiratory failure (0.8%).

Permanent discontinuation of LENVIMA due to an adverse reaction occurred in 23% of patients. Adverse reactions which resulted in permanent discontinuation of LENVIMA in $>0.5\%$ of patients included fatigue (1.6%), cardiac failure (1.1%), hyponatremia (1.1%), pneumonia (1.1%), decreased ejection fraction (0.8%), increased lipase (0.8%), pneumonitis (0.8%), proteinuria (0.8%) and rash (0.8%).

Dosage interruptions of WELIREG due to an adverse reaction occurred in 69% of patients. Adverse reactions which required dosage interruption in $>3\%$ of patients included fatigue (14%), diarrhea (12%), anemia (9%), vomiting (9%),

hypertension (9%), nausea (8%), decreased appetite (5%), abdominal pain (4.6%), COVID-19 (4.6%), musculoskeletal pain (4.1%), pneumonia (3.5%), hypoxia (3.5%) and hemorrhage (3.5%).

Dosage interruptions of LENVIMA due to an adverse reaction occurred in 72% of patients. The most common adverse reactions resulting in dosage interruption of LENVIMA (>3%) were fatigue (15%), hypertension (14%), diarrhea (13%), nausea (10%), vomiting (10%), anemia (8%), proteinuria (7%), decreased appetite (6%), COVID-19 (5%), musculoskeletal pain (4.3%), abdominal pain (4.3%), rash (4.3%), pneumonia (3.5%), stomatitis (3.5%) and hemorrhage (3.2%).

Dose reductions of WELIREG due to an adverse reaction occurred in 35% of patients. Adverse reactions which required dose reductions of WELIREG in >2% of patients included fatigue (7%), hypoxia (7%), anemia (6%), diarrhea (3%) and dyspnea (2.4%).

Dose reductions of LENVIMA due to an adverse reaction occurred in 67% of patients. Adverse reactions which required dose reductions of LENVIMA in >2% of patients included fatigue (20%), diarrhea (13%), hypertension (12%), proteinuria (9%), decreased appetite (8%), nausea (6%), rash (6%), vomiting (4.1%), anemia (3.5%), decreased weight (3.5%), abdominal pain (3%), increased alanine aminotransferase (ALT) (2.7%), stomatitis (2.7%), musculoskeletal pain (2.4%) and hypothyroidism (2.2%).

The most common ($\geq 25\%$) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG in combination with LENVIMA were decreased hemoglobin, fatigue, increased AST, hypertension, increased ALT, musculoskeletal pain, diarrhea, decreased lymphocytes, decreased sodium, increased creatinine, nausea, hypothyroidism, decreased appetite, decreased platelets, increased potassium, increased lipase, proteinuria, decreased magnesium, decreased calcium, increased activated partial thromboplastin time, rash, vomiting, decreased weight, constipation, abdominal pain and stomatitis.

Clinically relevant adverse reactions occurring in <15% of patients who received WELIREG in combination with LENVIMA included COVID-19 (14%), dysphonia (14%), dysgeusia (14%), urinary tract infection (14%), pruritus (12%), pyrexia (11%) and arrhythmia (9%).

About renal cell carcinoma

Renal cell carcinoma is the most common type of kidney cancer, with about nine out of 10 kidney cancer diagnoses being RCC. In 2024, there were an estimated 442,570 new cases of kidney cancer and 144,871 deaths from the disease worldwide. Renal cell carcinoma is about twice as common in men as in women. Cases of RCC might be discovered incidentally during imaging tests for other reasons. Approximately 32% of patients with kidney cancer are diagnosed at a regional or metastatic stage. Clear cell renal cell carcinoma, which accounts for about 70% of RCC diagnoses, is the most common subtype.

About Merck's research in genitourinary cancers

Merck is advancing research aimed at helping transform the treatment landscape and broaden options for people with genitourinary (GU) cancers, including bladder, kidney and prostate cancers. Globally, GU cancers account for an estimated 2.6 million new cancer diagnoses each year, equaling over 1 in 8 of all cancer incidences. Through a robust clinical development program with more than 50 ongoing clinical trials evaluating more than 22,000 patients around the world, Merck is investigating the potential of several portfolio medicines and pipeline assets, leveraging multiple novel combination strategies, across various stages of disease, to help address unmet needs in GU cancers.

About WELIREG® (belzutifan) 40 mg tablets, for oral use

WELIREG, Merck's first-in-class hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor, is an orally administered small-molecule that in conditions of hypoxia or impairment of VHL protein function, blocks HIF-2α and HIF-1β interaction, which may reduce the transcription and expression of HIF-2α target genes associated with cellular proliferation, angiogenesis and tumor growth. By inhibiting HIF-2α signaling, WELIREG may disrupt key pathways certain tumors may use to adapt to low-oxygen conditions, including those that help promote abnormal blood vessel formation and support tumor survival.

WELIREG has received prior regulatory approvals in certain patients with advanced renal cell carcinoma with a clear cell component (ccRCC) and adjuvant ccRCC in combination with KEYTRUDA, von Hippel-Lindau (VHL) disease-associated tumors and pheochromocytoma or paraganglioma (PPGL). As part of a broader clinical program, Merck continues to research WELIREG for people with RCC and selected solid tumors across different treatment settings, to further understand where WELIREG may provide clinical benefit.

Indications for WELIREG (belzutifan) in the U.S.

von Hippel-Lindau (VHL) disease

WELIREG is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Renal Cell Carcinoma with a Clear Cell Component (ccRCC)

WELIREG, in combination with KEYTRUDA or KEYTRUDA QLEX, is indicated for the adjuvant treatment of adult patients with ccRCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

WELIREG, in combination with LENVIMA, is indicated for the treatment of adult patients with advanced ccRCC following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

WELIREG, as monotherapy, is indicated for the treatment of adult patients with advanced ccRCC following a PD-1 or PD-L1 inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).

Pheochromocytoma or Paraganglioma (PPGL)

WELIREG is indicated for the treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL).

Selected Safety Information for WELIREG

Warning: Embryo-Fetal Toxicity

Exposure to WELIREG during pregnancy can cause embryo-fetal harm. Verify pregnancy status prior to the initiation of WELIREG. Advise patients of these risks and the need for effective non-hormonal contraception as WELIREG can render some hormonal contraceptives ineffective.

Anemia

WELIREG can cause severe anemia that can require blood transfusion.

Monitor for anemia before initiation of, and periodically throughout, treatment with WELIREG. Transfuse patients as clinically indicated. Withhold, reduce dose, or permanently discontinue WELIREG based on severity.

In LITESPARK-004 (N=61), decreased hemoglobin occurred in 93% of patients with VHL disease and 7% had Grade 3 events. Median time to onset of anemia was 31 days (range: 1 day to 8.4 months).

The safety of erythropoiesis-stimulating agents (ESAs) for treatment of anemia in patients with VHL disease treated with WELIREG has not been established.

In LITESPARK-005, in patients receiving WELIREG for advanced ccRCC (n=372), decreased hemoglobin occurred in 88% of patients with advanced ccRCC and 29% had Grade 3 events. Median time to onset of anemia was 29 days (range: 1 day to 16.6 months). Of the patients with anemia, 22% received transfusions only, 20% received ESAs only, and 12% received both transfusion and ESAs.

In LITESPARK-022, in patients receiving WELIREG in combination with KEYTRUDA for adjuvant treatment for ccRCC (n=915), decreased hemoglobin occurred in 95% of patients and 11% had Grade 3 or higher events. Median time to onset of anemia was 42 days (range: 1 day to 11.1 months). Of the patients with anemia, 5% received transfusions only, 8% received ESAs only, and 1.3% received both transfusion and ESAs.

In LITESPARK-011, in patients receiving WELIREG in combination with LENVIMA for advanced ccRCC (n=370),

decreased hemoglobin occurred in 87% of patients and 20% had Grade 3 events or required transfusion. Median time to onset of anemia was 56 days (range: 1 day to 33 months). Of the patients with anemia, 15% of patients received transfusions only, 22% received ESAs only, and 8% received both transfusion and ESAs.

In LITESPARK-015 (n=72), anemia occurred in 96% of patients with PPGL and 22% had Grade 3 events. Median time to onset of anemia was 29 days (range: 1 day to 22.1 months). Of the patients with anemia, 20% received transfusions only, 26% received ESAs only, and 6% received both transfusion and ESAs.

Hypoxia

WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization.

Monitor oxygen saturation before initiation of, and periodically throughout, treatment. For decreased oxygen saturation with exercise (e.g., pulse oximeter <88% or PaO₂ ≤55 mm Hg), consider withholding WELIREG until pulse oximetry with exercise is greater than 88%, then resume at the same or a reduced dose. For decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO₂ ≤55 mm Hg) or when urgent intervention is indicated, withhold WELIREG until resolved and resume at a reduced dose or discontinue. For life-threatening or recurrent symptomatic hypoxia, permanently discontinue WELIREG. Advise patients to report signs and symptoms of hypoxia immediately to a health care provider.

In LITESPARK-004, hypoxia occurred in 1.6% of patients with VHL disease.

In LITESPARK-005, in patients receiving WELIREG as monotherapy for advanced ccRCC, hypoxia occurred in 15% of patients and 10% had Grade 3 events. Of the patients with hypoxia, 69% were treated with oxygen therapy. Median time to onset of hypoxia was 30.5 days (range: 1 day to 21.1 months).

In LITESPARK-022, in patients receiving WELIREG in combination with KEYTRUDA for adjuvant treatment for ccRCC, hypoxia occurred in 7% of patients and 5% had Grade 3 or higher events. Of the patients with hypoxia, 47% were treated with oxygen therapy. Median time to onset of hypoxia was 93 days (range: 9 days to 11.7 months).

In LITESPARK-011, in patients receiving WELIREG in combination with LENVIMA for advanced ccRCC, hypoxia occurred in 16% of patients and 12% had Grade 3-4 events. Of the patients with hypoxia, 62% of patients were treated with oxygen therapy. Median time to onset was 63 days (range: 4 days to 25 months).

In LITESPARK-015, hypoxia occurred in 13% of patients with PPGL and 10% had Grade 3 hypoxia. Median time to onset of hypoxia was 35 days (range: 6 days to 23.9 months). Of the patients with hypoxia, 67% were treated with oxygen therapy.

Cardiac Dysfunction with Concomitant Use of WELIREG and LENVIMA

Serious cardiac dysfunction, including heart failure with reduced left ventricular ejection fraction (LVEF), and cardiomyopathy, can occur with WELIREG in combination with LENVIMA. The safety of WELIREG in combination with LENVIMA has not been established in patients with LVEF below 50%.

In patients treated with WELIREG in combination with LENVIMA in the LITESPARK-011 trial, Grade 3 or higher cardiac dysfunction adverse events occurred in 6% of patients. The median time to onset of Grade 3 or higher cardiac dysfunction was 26 weeks (range: 1 to 192 weeks). An absolute decrease in LVEF >20% with or without clinical symptoms occurred in 6% of patients. The median time to onset of LVEF decrease >20% was 29 weeks (range: 2 to 192 weeks).

Consider obtaining a baseline echocardiogram or Multigated Acquisition (MUGA) imaging. Monitor patients for symptoms or signs of heart failure and if present, reassess LVEF. Withhold and resume at a reduced dose upon recovery to baseline or Grade 1 or permanently discontinue WELIREG in combination with LENVIMA based on severity.

Embryo-Fetal Toxicity

Based on findings in animals, WELIREG can cause fetal harm when administered to a pregnant woman.

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose. WELIREG can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.

Adverse Reactions

Adverse Reactions in LITESPARK-004 (VHL disease)

Serious adverse reactions occurred in 15% of patients, including anemia, hypoxia, anaphylaxis reaction, retinal detachment, and central retinal vein occlusion (1 patient each).

WELIREG was permanently discontinued due to adverse reactions in 3.3% of patients for dizziness and opioid overdose (1.6% each).

Dosage interruptions due to an adverse reaction occurred in 39% of patients. Those which required dosage interruption in >2% of patients were fatigue, decreased hemoglobin, anemia, nausea, abdominal pain, headache, and influenza-like illness.

Dose reductions due to an adverse reaction occurred in 13% of patients. The most frequently reported adverse reaction which required dose reduction was fatigue (7%).

The most common adverse reactions ($\geq 25\%$), including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin (93%), fatigue (64%), increased creatinine (64%), headache (39%), dizziness (38%), increased glucose (34%), and nausea (31%).

Adverse Reactions in LITESPARK-022 (Adjuvant ccRCC)

Serious adverse reactions occurred in 30% of patients receiving WELIREG in combination with KEYTRUDA. The most frequently reported serious adverse reactions ($\geq 1\%$) were pneumonia (2%), hypoxia (1.9%), pneumonitis (1.6%), arrhythmia (1.5%), diarrhea (1.1%), and acute kidney injury (1.1%). Fatal adverse reactions occurred in 1.1% of patients who received WELIREG in combination with KEYTRUDA, including sepsis (0.1%).

WELIREG was permanently discontinued due to adverse reactions in 27% of patients. Adverse reactions which resulted in permanent discontinuation of WELIREG in $\geq 1\%$ of patients included anemia (4%), fatigue (2.2%), rash (2%), increased alanine aminotransferase (ALT) (1.7%), hypoxia (1.6%), diarrhea (1.4%), pneumonitis (1.3%), increased aspartate aminotransferase (AST) (1.1%), and hepatic function abnormal (1%).

Dosage interruptions of WELIREG due to an adverse reaction occurred in 52% of patients. Of the patients who received WELIREG in combination with KEYTRUDA, 30% were ≥ 65 years old and 5% were ≥ 75 years old. Dose interruptions of WELIREG occurred in 57% of patients ≥ 65 years of age and in 49% of younger patients. Adverse reactions which required dosage interruption of WELIREG in $\geq 2\%$ of patients included anemia (25%), fatigue (3.7%), increased ALT (3.5%), diarrhea (3.4%), increased AST (3.4%), COVID-19 (2.6%), hypoxia (2.5%), pyrexia (2.5%), musculoskeletal pain (2.1%), and rash (2.1%).

Dose reductions of WELIREG due to an adverse reaction occurred in 34% of patients. Dose reductions of WELIREG occurred in 39% of patients ≥ 65 years of age and in 32% of younger patients. Adverse reactions which required dose reduction in $\geq 3\%$ of patients included anemia (17%), hypoxia (3.5%), increased ALT (3.2%), and fatigue (3.1%).

The most common ($\geq 25\%$) adverse reactions, including laboratory abnormalities, in patients who received WELIREG in combination with KEYTRUDA were decreased hemoglobin (95%), increased ALT (57%), fatigue (49%), increased AST (46%), decreased lymphocytes (38%), and increased alkaline phosphatase (29%).

Adverse Reactions in LITESPARK-011 (Advanced ccRCC)

Serious adverse reactions occurred in 54% of patients who received WELIREG in combination with LENVIMA. Serious adverse reactions in $\geq 2\%$ of patients included hypoxia (6%), pneumonia (5%), hyponatremia (3.2%), acute kidney injury (3%), hemorrhage (2.7%), anemia (2.7%), cardiac failure (2.4%), and diarrhea (2.4%).

Fatal adverse reactions occurred in 5% of patients who received WELIREG in combination with LENVIMA, including sepsis (0.8%), pneumonia (0.5%), pneumonitis (0.5%), respiratory failure (0.5%), and one case (0.3%) each of acute cholecystitis, acute respiratory distress syndrome, pulmonary edema, embolic cerebral infarction, hemorrhage, postoperative wound complication, thrombotic microangiopathy and upper respiratory tract infection.

Permanent discontinuation of WELIREG due to an adverse reaction occurred in 17% of patients. Adverse reactions which resulted in permanent discontinuation of WELIREG in >0.5% of patients included hypoxia (2.2%), pneumonia (1.1%), fatigue (0.8%), hyponatremia (0.8%), pneumonitis (0.8%), and respiratory failure (0.8%)

Dosage interruptions of WELIREG due to an adverse reaction occurred in 69% of patients. Adverse reactions which required dosage interruption in >3% of patients included fatigue (14%), diarrhea (12%), anemia (9%), vomiting (9%), hypertension (9%), nausea (8%), decreased appetite (5%), abdominal pain (4.6%), COVID-19 (4.6%), musculoskeletal pain (4.1%), and pneumonia (3.5%), hypoxia (3.5%) and hemorrhage (3.5%).

Dose reductions of WELIREG due to an adverse reaction occurred in 35% of patients. Adverse reactions which required dose reductions in >2% of patients included fatigue (7%), hypoxia (7%), anemia (6%), diarrhea (3%), and dyspnea (2.4%).

The most common ($\geq 25\%$) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG in combination with LENVIMA were decreased hemoglobin, fatigue, increased AST, hypertension, increased ALT, musculoskeletal pain, diarrhea, decreased lymphocytes, decreased sodium, increased creatinine, nausea, hypothyroidism, decreased appetite, decreased platelets, increased potassium, increased lipase, proteinuria, decreased magnesium, decreased calcium, increased activated partial thromboplastin time, rash, vomiting, decreased weight, constipation, abdominal pain, and stomatitis.

Adverse Reactions in LITESPARK-005 (Advanced ccRCC)

Serious adverse reactions occurred in 38% of patients. The most frequently reported serious adverse reactions ($\geq 2\%$) were hypoxia (7%), anemia (5%), pneumonia (3.5%), hemorrhage (3%), and pleural effusion (2.2%). Fatal adverse reactions occurred in 3.2% of patients who received WELIREG, including sepsis (0.5%) and hemorrhage (0.5%).

WELIREG was permanently discontinued due to adverse reactions in 6% of patients. Adverse reactions which resulted in permanent discontinuation ($\geq 0.5\%$) were hypoxia (1.1%), anemia (0.5%), and hemorrhage (0.5%).

Dosage interruptions due to an adverse reaction occurred in 39% of patients. Of the patients who received WELIREG, 28% were 65 to 74 years, and 10% were 75 years and over. Dose interruptions occurred in 48% of

patients ≥ 65 years of age and in 34% of younger patients. Adverse reactions which required dosage interruption in $\geq 2\%$ of patients were anemia (8%), hypoxia (5%), COVID-19 (4.3%), fatigue (3.2%), and hemorrhage (2.2%).

Dose reductions due to an adverse reaction occurred in 13% of patients. Dose reductions occurred in 18% of patients ≥ 65 years of age and in 10% of younger patients. The most frequently reported adverse reactions which required dose reduction ($\geq 1\%$) were hypoxia (5%) and anemia (3.2%).

The most common adverse reactions ($\geq 25\%$), including laboratory abnormalities, were decreased hemoglobin (88%), fatigue (43%), musculoskeletal pain (34%), increased creatinine (34%), decreased lymphocytes (34%), increased alanine aminotransferase (32%), decreased sodium (31%), increased potassium (29%), and increased aspartate aminotransferase (27%).

Adverse Reactions in LITESPARK-015 (PPGL)

Serious adverse reactions occurred in 36% of patients. The most frequently reported serious adverse reactions ($\geq 2\%$) were anemia and hypertension (4.2% each) and pyelonephritis, pneumonia, hypoxia, dyspnea and hemorrhage (2.8% each).

WELIREG was permanently discontinued due to adverse reactions in 2 patients (2.8%). Adverse reactions which resulted in permanent discontinuation were increased alanine aminotransferase and paraparesis (1.4% each).

Dosage interruptions due to an adverse reaction occurred in 40% of patients. Of the patients who received WELIREG, 13% were ≥ 65 years old and 4.2% were ≥ 75 years. Adverse reactions which required dosage interruption in $>3\%$ of patients were hypoxia, nausea, and fatigue (4.2% each).

Dose reductions due to an adverse reaction occurred in 14% of patients. The most frequently reported adverse reaction which required dose reduction was hypoxia (4.2%).

The most common ($\geq 25\%$) adverse reactions, including laboratory abnormalities, that occurred in patients were anemia (96%), fatigue (56%), musculoskeletal pain (56%), decreased lymphocytes (54%), increased alanine aminotransferase (51%), increased aspartate aminotransferase (42%), increased calcium (34%), dyspnea (33%), increased potassium (31%), decreased leukocytes (30%), headache (29%), increased alkaline phosphatase (25%), dizziness (26%) and nausea (25%).

Drug Interactions

Coadministration of WELIREG with inhibitors of UGT2B17 or CYP2C19 increases plasma exposure of belzutifan, which may increase the incidence and severity of adverse reactions. Monitor for anemia and hypoxia and reduce the dosage of WELIREG as recommended.

Coadministration of WELIREG with CYP3A4 substrates decreases concentrations of CYP3A4 substrates, which may reduce the efficacy of these substrates or lead to therapeutic failures. Avoid coadministration with sensitive CYP3A4 substrates. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information. Coadministration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding.

Lactation

Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with WELIREG and for 1 week after the last dose.

Refer to the Prescribing Information of the individual therapeutic agents used in combination with WELIREG for lactation information. When used in combination, advise patients not to breastfeed during treatment and for the longest post-treatment duration recommended in the Prescribing Information of the individual products.

Females and Males of Reproductive Potential

WELIREG can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG.

Use of WELIREG may reduce the efficacy of hormonal contraceptives. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.

Based on findings in animals, WELIREG may impair fertility in males and females of reproductive potential and the reversibility of this effect is unknown.

Refer to the Prescribing Information of the individual therapeutic agents used in combination with WELIREG for pregnancy information.

Refer to the Prescribing Information of the individual therapeutic agents used in combination with WELIREG for contraception and infertility information. When used in combination, advise patients to use effective contraception during treatment and for the longest post-treatment duration recommended in the Prescribing Information of the individual products.

Pediatric Use

Use of WELIREG in pediatric patients aged 12 years and older for PPGL is supported by evidence from an adequate and well-controlled study of WELIREG in adults with additional pharmacokinetic data demonstrating that belzutifan

exposure is predicted to be within range of that observed in adults, and that the course of locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma is sufficiently similar in adults and pediatric patients to allow extrapolation of data in adults to pediatric patients.

The safety and effectiveness of WELIREG have not been established in patients with VHL or ccRCC, or in pediatric patients younger than 12 years of age with PPGL.

Renal Impairment

For patients with severe renal impairment (eGFR 15-29 mL/min estimated by MDRD), monitor for increased adverse reactions and modify the dosage as recommended.

Hepatic Impairment

For patients with moderate and severe hepatic impairment, monitor for increased adverse reactions and modify the dosage as recommended.

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

LENVIMA, discovered and developed by Eisai, is an orally available multiple receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). LENVIMA inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1-4, the platelet derived growth factor receptor alpha (PDGFR α), KIT, and RET. In syngeneic mouse tumor models, LENVIMA 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. The combination of LENVIMA and everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and tumor volume in mouse xenograft models of human renal cell cancer greater than each drug alone.

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

- For the treatment of adult patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC).
- In combination with KEYTRUDA or KEYTRUDA QLEX, for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
- In combination with WELIREG, for the treatment of adult patients with advanced renal cell carcinoma with a clear cell component (ccRCC) following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

- In combination with everolimus, for the treatment of adult patients with advanced RCC following one prior anti-angiogenic therapy.
- For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC).
- In combination with KEYTRUDA or KEYTRUDA QLEX, for the treatment of patients with advanced endometrial carcinoma (EC) that is mismatch repair proficient (pMMR) or not microsatellite instability-high (MSI-H), as determined by an FDA-authorized test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Selected Safety Information for LENVIMA

Warnings and Precautions

Hypertension. In differentiated thyroid cancer (DTC), hypertension occurred in 73% of patients on LENVIMA (44% Grade 3; <1% Grade 4). In advanced renal cell carcinoma (RCC), hypertension occurred in 42% of patients on LENVIMA + everolimus (13% Grade 3). Systolic blood pressure ≥ 160 mmHg occurred in 29% of patients, and 21% had diastolic blood pressure ≥ 100 mmHg. In unresectable hepatocellular carcinoma (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, including heart failure with reduced left ventricular ejection fraction (LVEF), and cardiomyopathy can occur with LENVIMA. The safety of LENVIMA either as monotherapy or in combination with WELIREG has not been established in patients with LVEF below 50%. In patients with DTC, RCC, and HCC treated with LENVIMA, Grade 3 or higher cardiac dysfunction adverse events occurred in 1% of patients. The median time to onset of Grade 3 or higher cardiac dysfunction was 35 weeks (range 7 to 63 weeks). An absolute decrease in LVEF $>20\%$ with or without clinical symptoms occurred in 1% of LENVIMA-treated patients. The median time to onset of LVEF decrease $>20\%$ was 33 weeks (range 4 to 83 weeks).

In patients treated with LENVIMA in combination with WELIREG for ccRCC, Grade 3 or higher cardiac dysfunction adverse events occurred in 6% of patients. The median time to onset of Grade 3 or higher cardiac dysfunction was 26 weeks (range 1 to 192 weeks). An absolute decrease in LVEF $>20\%$ with or without clinical symptoms occurred in 6% of patients and the median time to onset of LVEF decrease $>20\%$ was 29 weeks (range: 2 to 192 weeks).

Consider obtaining a baseline echocardiogram or Multigated Acquisition (MUGA) imaging. Monitor patients for symptoms or signs of heart failure and if present, reassess LVEF. Withhold and resume at a reduced dose upon recovery to baseline or Grade 1 or permanently discontinue LENVIMA 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.

Arterial thrombotic events of any severity occurred in 5% of patients with RCC receiving LENVIMA + KEYTRUDA, including myocardial infarction (3.4%) and cerebrovascular accident (2.3%).

Permanently discontinue following an arterial thrombotic event. The safety of resuming after an arterial thromboembolic event has not been established and LENVIMA has not been studied in patients who have had an arterial thromboembolic event within the previous 6 months.

Hepatotoxicity. Serious hepatic adverse reactions occurred in 1.4% of LENVIMA-treated patients with malignancies other than HCC; 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) and Grade 3-5 hepatic failure occurred in 3% of 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 LENVIMA 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. In DTC and HCC, diarrhea occurred in 49% of LENVIMA-treated patients (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. In 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 QTc 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 QTc interval. Withhold and resume at reduced dose upon recovery based on severity.

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

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). In 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, hemorrhagic events, of any grade, occurred in 29% of patients treated with LENVIMA as a single agent or in combination with everolimus. The most frequently reported hemorrhagic events ($\geq 5\%$) 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 with 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 ATC have not been established.

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

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

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

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

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

Perform an oral examination prior to treatment with LENVIMA and periodically during LENVIMA treatment. Advise patients regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on LENVIMA treatment, particularly in patients at higher risk. Withhold LENVIMA for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ.

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

Embryo-Fetal Toxicity. Based on its mechanism of action and data from animal reproduction studies, LENVIMA can cause fetal harm when administered to pregnant women. In animal reproduction studies, oral administration of LENVIMA 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 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, diarrhea (67% each), 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, and dysphonia (31% each). The most common serious adverse reactions ($\geq 2\%$) were pneumonia (4%), hypertension, and dehydration (3% each). 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, and diarrhea (10% each); the most common adverse reactions ($\geq 1\%$) resulting in discontinuation of LENVIMA were hypertension and asthenia (1% each).

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

Fatal adverse reactions occurred in 4.3% of patients receiving LENVIMA + KEYTRUDA, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm and subarachnoid hemorrhage.

Serious adverse reactions occurred in 51% of patients receiving LENVIMA + KEYTRUDA; the most common ($\geq 2\%$) were hemorrhagic events (5%), diarrhea (4%), hypertension, myocardial infarction, pneumonitis, vomiting (3% each), acute kidney injury, adrenal insufficiency, dyspnea, and pneumonia (2% each).

Permanent discontinuation of LENVIMA, KEYTRUDA, or both due to an adverse reaction occurred in 37% of patients; 26% LENVIMA only, 29% KEYTRUDA only, and 13% both. The most common adverse reactions ($\geq 2\%$)

leading to permanent discontinuation of LENVIMA, KEYTRUDA, or both were pneumonitis, myocardial infarction, hepatotoxicity, acute kidney injury, rash (3% each), and diarrhea (2%).

Dose interruptions of LENVIMA, KEYTRUDA, or both due to an adverse reaction occurred in 78% of patients receiving LENVIMA + KEYTRUDA. LENVIMA was interrupted in 73% of patients and both drugs were interrupted in 39% of patients. LENVIMA was dose reduced in 69% of patients. The most common adverse reactions ($\geq 5\%$) resulting in dose reduction or interruption of LENVIMA were diarrhea (26%), fatigue (18%), hypertension (17%), proteinuria (13%), decreased appetite (12%), palmar-plantar erythrodysesthesia (11%), nausea, stomatitis (9% each), musculoskeletal pain, rash (8% each), increased lipase (7%), abdominal pain and vomiting (6% each), increased ALT, and increased amylase (5% each).

In RCC, the most common ($\geq 25\%$) adverse reactions, that occurred in patients who received LENVIMA + WELIREG were anemia (70%), fatigue (68%), hypertension (60%), musculoskeletal pain (55%), diarrhea (54%), nausea, hypothyroidism, (42% each), decreased appetite (41%), proteinuria (38%), rash (33%), vomiting (32%), decreased weight (29%), constipation (27%), abdominal pain (26%), and stomatitis (25%).

Fatal adverse reactions occurred in 5% of patients who received LENVIMA + WELIREG, including sepsis (0.8%), pneumonia, pneumonitis, respiratory failure (0.5% each), and one case (0.3%) each of acute cholecystitis, acute respiratory distress syndrome, pulmonary edema, embolic cerebral infarction, hemorrhage, postoperative wound complication, thrombotic microangiopathy, and upper respiratory tract infection.

Serious adverse reactions occurred in 54% of patients who received LENVIMA in combination with WELIREG. Serious adverse reactions in ($\geq 2\%$) of patients included hypoxia (6%), pneumonia (5%), hyponatremia (3.2%), acute kidney injury (3%), hemorrhage, anemia (2.7% each), cardiac failure, and diarrhea (2.4% each).

Permanent discontinuation of LENVIMA due to an adverse reaction occurred in 23% of patients. Adverse reactions which resulted in permanent discontinuation of LENVIMA in ($>0.5\%$) of patients included fatigue (1.6%), cardiac failure, hyponatremia, pneumonia (1.1% each), decreased ejection fraction, increased lipase, pneumonitis, proteinuria, and rash (0.8% each).

Dosage interruptions of LENVIMA due to an adverse reaction occurred in 72% of patients. The most common adverse reactions requiring dose interruption ($>3\%$) were fatigue (15%), hypertension (14%), diarrhea (13%), nausea, vomiting (10% each), anemia (8%), proteinuria (7%), decreased appetite (6%), COVID-19 (5%), musculoskeletal pain, abdominal pain, rash (4.3% each), pneumonia, stomatitis (3.5% each), and hemorrhage (3.2%).

Dose reductions of LENVIMA due to an adverse reaction occurred in 67% of patients. The most common adverse reactions which required dose reductions ($>2\%$) were fatigue (20%), diarrhea (13%), hypertension (12%), proteinuria

(9%), decreased appetite (8%), nausea, rash (6% each), vomiting (4.1%), anemia, decreased weight (3.5% each), abdominal pain (3%) increased ALT, stomatitis (2.7% each), musculoskeletal pain (2.4%), and hypothyroidism (2.2%).

In LENVIMA + everolimus-treated patients, the most common adverse reactions ($\geq 30\%$) observed were diarrhea (81%), fatigue (73%), arthralgia/myalgia (55%), decreased appetite (53%), vomiting (48%), nausea (45%), stomatitis (44%), hypertension, peripheral edema (42% each), cough, abdominal pain (37% each), dyspnea, rash (35% each), 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, diarrhea, vomiting, and dyspnea (5% each). 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, vomiting (6% each), nausea, and proteinuria (5% each). 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, decreased weight (31% each), 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, ascites (3% each), 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, diarrhea (8% each), 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 hepatic encephalopathy (2%), fatigue, hyperbilirubinemia, and hepatic failure (1% each).

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

Fatal adverse reactions among these patients occurred in 4.7% of those treated with LENVIMA and KEYTRUDA, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving LENVIMA and KEYTRUDA. Serious adverse reactions with frequency $\geq 3\%$ were hypertension (4.4%), and urinary tract infection (3.2%).

Discontinuation of LENVIMA due to an adverse reaction occurred in 26% of these patients. The most common ($\geq 1\%$) adverse reactions leading to discontinuation of LENVIMA were hypertension (2%), asthenia (1.8%), diarrhea, decreased appetite, proteinuria, and vomiting (1.2% each).

Dose reductions of LENVIMA due to adverse reactions occurred in 67% of patients. The most common ($\geq 5\%$) adverse reactions resulting in dose reduction of LENVIMA were hypertension (18%), diarrhea (11%), palmar-plantar erythrodysesthesia syndrome (9%), proteinuria, fatigue (7% each), decreased appetite (6%), asthenia, and weight decreased (5% each).

Dose interruptions of LENVIMA due to an adverse reaction occurred in 58% of these patients. The most common ($\geq 2\%$) adverse reactions leading to interruption of LENVIMA were hypertension, diarrhea (11% each), proteinuria (6%), decreased appetite, vomiting (5% each), increased alanine aminotransferase, fatigue, nausea (3.5% each), abdominal pain (2.9%), weight decreased, urinary tract infection (2.6% each), increased aspartate aminotransferase, asthenia (2.3% each), and palmar-plantar erythrodysesthesia (2%).

Use in Specific Populations

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

Verify the pregnancy status of females of reproductive potential prior to initiating LENVIMA.

LENVIMA may impair fertility in males and females of reproductive potential.

No dose adjustment is recommended for patients with mild (creatinine clearance [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.

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 endometrial carcinoma and severe hepatic impairment.

For more information about LENVIMA, please see available full Prescribing Information.

About KEYTRUDA® (pembrolizumab) injection for intravenous use, 100 mg

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

Merck has the industry's largest immuno-oncology clinical research program. There are currently more than 2,800 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.

About KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph) injection for subcutaneous use, 165 mg + 2,000 units/mL

KEYTRUDA QLEX is a fixed-combination drug product of pembrolizumab and berahyaluronidase alfa.

Pembrolizumab is a programmed death receptor-1 (PD-1) blocking antibody and berahyaluronidase alfa enhances dispersion and permeability to enable subcutaneous administration of pembrolizumab. KEYTRUDA QLEX is administered as a subcutaneous injection into the thigh or abdomen, avoiding the 5 cm area around the navel, over one minute every three weeks (2.4 mL) or over two minutes every six weeks (4.8 mL).

Selected Indications in the U.S. for KEYTRUDA® (pembrolizumab) and KEYTRUDA QLEX™ (pembrolizumab and berahyaluronidase alfa-pmph)

Renal Cell Carcinoma

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

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with LENVIMA, for the first-line treatment of adult patients with advanced RCC.

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

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with WELIREG, for the adjuvant treatment of adult patients with RCC with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

See additional selected indications in the U.S. for KEYTRUDA and KEYTRUDA QLEX after the Selected Safety Information.

Selected Safety Information for KEYTRUDA and KEYTRUDA QLEX

Contraindications

KEYTRUDA QLEX is contraindicated in patients with known hypersensitivity to berahyaluronidase alfa, hyaluronidase or to any of its excipients.

Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA and KEYTRUDA QLEX are monoclonal antibodies that belong 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. Important immune-mediated adverse reactions listed here may not include all possible severe and fatal immune-mediated adverse reactions.

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

Withhold or permanently discontinue KEYTRUDA and KEYTRUDA QLEX depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA and KEYTRUDA QLEX require 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 and KEYTRUDA QLEX 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. Immune-mediated pneumonitis occurred in 5% (13/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including fatal (0.4%), Grade 3 (2%), and Grade 2 (1.2%) adverse reactions.

Pneumonitis occurred in 7% (41/580) of adult patients with resected NSCLC who received KEYTRUDA as a single agent for adjuvant treatment of NSCLC, including fatal (0.2%), Grade 4 (0.3%), and Grade 3 (1%) adverse reactions. Patients received high-dose corticosteroids for a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to discontinuation of KEYTRUDA in 26 (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 63% discontinued KEYTRUDA, and 71% had resolution.

Immune-Mediated Colitis

KEYTRUDA and KEYTRUDA QLEX 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. Immune-mediated colitis occurred in 1.2% (3/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 3 (0.8%) and Grade 2 (0.4%) adverse reactions.

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA and KEYTRUDA QLEX 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. Immune-mediated hepatitis occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (0.4%) adverse reactions.

KEYTRUDA With Axitinib or KEYTRUDA QLEX With Axitinib

KEYTRUDA and KEYTRUDA QLEX, when either is used 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 or KEYTRUDA QLEX and axitinib, and consider administering corticosteroids as needed.

With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased alanine aminotransferase (ALT) (20%) and increased aspartate aminotransferase (AST) (13%) were seen at a higher frequency compared to KEYTRUDA alone. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥ 3 times upper limit of normal (ULN) (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT ≥ 3 times ULN was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both. All patients with a recurrence of ALT ≥ 3 ULN subsequently recovered from the event.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

KEYTRUDA and KEYTRUDA QLEX can cause primary or secondary adrenal insufficiency. For Grade 2 or higher, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA and KEYTRUDA QLEX 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. Adrenal insufficiency occurred in 2% (5/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 3 (0.4%) and Grade 2 (0.8%) adverse reactions.

Hypophysitis

KEYTRUDA and KEYTRUDA QLEX 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 and KEYTRUDA QLEX 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 and KEYTRUDA QLEX 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 and KEYTRUDA QLEX 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 hyperthyroidism was higher in 580 patients with resected NSCLC, occurring in 11% of patients receiving KEYTRUDA as a single agent as adjuvant treatment, including Grade 3 (0.2%) hyperthyroidism. The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC, occurring in 22% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) hypothyroidism.

Thyroiditis occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (0.4%). Hyperthyroidism occurred in 8% (20/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (3.2%). Hypothyroidism occurred in 14% (35/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 2 (11%).

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 and KEYTRUDA QLEX depending on severity. Type 1 DM occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. It led to permanent discontinuation in <0.1% (1) and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Type 1 DM occurred in 0.4% (1/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy.

Immune-Mediated Nephritis With Renal Dysfunction

KEYTRUDA and KEYTRUDA QLEX 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 and KEYTRUDA QLEX 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 and KEYTRUDA QLEX 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. Immune-mediated dermatologic adverse reactions occurred in 1.6% (4/251) of patients receiving KEYTRUDA QLEX in combination with chemotherapy, including Grade 4 (0.8%) and Grade 3 (0.8%) adverse reactions.

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, KEYTRUDA QLEX, 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 (2.8%), 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, other transplant (including corneal graft) rejection; Other: Myocarditis-Myositis-Myasthenia Gravis (or Myasthenia-Like) Overlap syndrome, reported as the co-occurrence of either two or all three adverse reactions.

Hypersensitivity and Infusion- or Administration-Related Reactions

KEYTRUDA and KEYTRUDA QLEX can cause severe or life-threatening administration-related reactions, including hypersensitivity and anaphylaxis. With KEYTRUDA and KEYTRUDA QLEX, monitor for signs and symptoms of infusion- and administration-related systemic reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Infusion-related reactions have been reported in 0.2% of 2799 patients receiving KEYTRUDA. 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. Hypersensitivity and administration related systemic reactions occurred in 3.2% (8/251) of patients receiving KEYTRUDA QLEX in combination with platinum doublet chemotherapy, including Grade 2 (2.8%). Interrupt injection (if not already fully administered) and resume if symptoms resolve for mild or moderate systemic reactions. For severe or life-threatening systemic reactions, stop injection and permanently discontinue KEYTRUDA QLEX.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti-PD-1/PD-L1 treatments. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti-PD-1/PD-L1 treatments 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 their mechanism of action, KEYTRUDA and KEYTRUDA QLEX can each 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 or KEYTRUDA QLEX and advise them to use effective contraception during treatment and for 4 months after the last dose.

Adverse Reactions

In study MK-3475A-D77, when KEYTRUDA QLEX was administered with chemotherapy in metastatic non-small cell lung cancer (NSCLC), serious adverse reactions occurred in 39% of patients. Serious adverse reactions in $\geq 1\%$ of patients who received KEYTRUDA QLEX were pneumonia (10%), thrombocytopenia (4%), febrile neutropenia (4%), neutropenia (2.8%), musculoskeletal pain (2%), pneumonitis (2%), diarrhea (1.6%), rash (1.2%), respiratory failure (1.2%), and anemia (1.2%). Fatal adverse reactions occurred in 10% of patients including pneumonia (3.2%), neutropenic sepsis (2%), death not otherwise specified (1.6%), respiratory failure (1.2%), parotitis (0.4%), pneumonitis (0.4%), pneumothorax (0.4%), pulmonary embolism (0.4%), neutropenic colitis (0.4%), and seizure (0.4%). KEYTRUDA QLEX was permanently discontinued due to an adverse reaction in 16% of 251 patients. Adverse reactions which resulted in permanent discontinuation of KEYTRUDA QLEX in $\geq 2\%$ of patients included pneumonia and pneumonitis. Dosage interruptions of KEYTRUDA QLEX due to an adverse reaction occurred in 45% of patients. Adverse reactions which required dosage interruption in $\geq 2\%$ of patients included neutropenia, anemia, thrombocytopenia, pneumonia, rash, and increased aspartate aminotransferase. The most common adverse reactions ($\geq 20\%$) were nausea (25%), fatigue (25%), and musculoskeletal pain (21%).

In KEYNOTE-006, KEYTRUDA was discontinued due to adverse reactions in 9% of 555 patients with advanced melanoma; adverse reactions leading to permanent discontinuation in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). The most common adverse reactions ($\geq 20\%$) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (21%).

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

In KEYNOTE-189, when KEYTRUDA was administered with pemetrexed and platinum chemotherapy in metastatic nonsquamous NSCLC, KEYTRUDA was discontinued due to adverse reactions in 20% of 405 patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). The most common adverse reactions ($\geq 20\%$) with KEYTRUDA were nausea (56%), fatigue (56%), constipation (35%), diarrhea (31%), decreased appetite (28%), rash (25%), vomiting (24%), cough (21%), dyspnea (21%), and pyrexia (20%).

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

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

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

In KEYNOTE-671, adverse reactions occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as single-agent adjuvant treatment, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.

The most common adverse reactions (reported in $\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy or chemoradiotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, insomnia, palmar-plantar erythrodysesthesia, urinary tract infection, hypothyroidism, radiation skin injury, dysphagia, dry mouth, and musculoskeletal pain.

In the neoadjuvant phase of KEYNOTE-671, when KEYTRUDA was administered in combination with platinum-

containing chemotherapy as neoadjuvant treatment, serious adverse reactions occurred in 34% of 396 patients. The most frequent ($\geq 2\%$) serious adverse reactions were pneumonia (4.8%), venous thromboembolism (3.3%), and anemia (2%). Fatal adverse reactions occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated lung disease (0.3%). Permanent discontinuation of any study drug due to an adverse reaction occurred in 18% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy; the most frequent adverse reactions ($\geq 1\%$) that led to permanent discontinuation of any study drug were acute kidney injury (1.8%), interstitial lung disease (1.8%), anemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).

Of the KEYTRUDA-treated patients who received neoadjuvant treatment, 6% of 396 patients did not receive surgery due to adverse reactions. The most frequent ($\geq 1\%$) adverse reaction that led to cancellation of surgery in the KEYTRUDA arm was interstitial lung disease (1%).

In the adjuvant phase of KEYNOTE-671, when KEYTRUDA was administered as a single agent as adjuvant treatment, serious adverse reactions occurred in 14% of 290 patients. The most frequent serious adverse reaction was pneumonia (3.4%). One fatal adverse reaction of pulmonary hemorrhage occurred. Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 12% of patients who received KEYTRUDA as a single agent, given as adjuvant treatment; the most frequent adverse reactions ($\geq 1\%$) that led to permanent discontinuation of KEYTRUDA were diarrhea (1.7%), interstitial lung disease (1.4%), increased aspartate aminotransferase (1%), and musculoskeletal pain (1%).

Adverse reactions observed in KEYNOTE-091 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). Two fatal adverse reactions of myocarditis occurred.

Adverse reactions observed in KEYNOTE-483 were generally similar to those occurring in other patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy.

In KEYNOTE-689, the most common adverse reactions ($\geq 20\%$) in patients receiving KEYTRUDA were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), dysphagia (29%), constipation (27%), hypothyroidism (26%), nausea (24%), rash (22%), dry mouth (22%), diarrhea (22%), and musculoskeletal pain (22%).

In the neoadjuvant phase of KEYNOTE-689, of the 361 patients who received at least one dose of single agent KEYTRUDA, 11% experienced serious adverse reactions. Serious adverse reactions that occurred in more than one patient were pneumonia (1.4%), tumor hemorrhage (0.8%), dysphagia (0.6%), immune-mediated hepatitis (0.6%), cellulitis (0.6%), and dyspnea (0.6%). Fatal adverse reactions occurred in 1.1% of patients, including respiratory failure, clostridium infection, septic shock, and myocardial infarction (one patient each). Permanent discontinuation

of KEYTRUDA due to an adverse reaction occurred in 2.8% of patients who received KEYTRUDA as neoadjuvant treatment. The most frequent adverse reaction which resulted in permanent discontinuation of neoadjuvant KEYTRUDA in more than one patient was arthralgia (0.6%).

Of the 361 patients who received KEYTRUDA as neoadjuvant treatment, 11% did not receive surgery. Surgical cancellation on the KEYTRUDA arm was due to disease progression in 4%, patient decision in 3%, adverse reactions in 1.4%, physician's decision in 1.1%, unresectable tumor in 0.6%, loss of follow-up in 0.3%, and use of non-study anti-cancer therapy in 0.3%.

Of the 323 KEYTRUDA-treated patients who received surgery following the neoadjuvant phase, 1.2% experienced delay of surgery (defined as on-study surgery occurring ≥ 9 weeks after initiation of neoadjuvant KEYTRUDA) due to adverse reactions, and 2.8% did not receive adjuvant treatment due to adverse reactions.

In the adjuvant phase of KEYNOTE-689, of the 255 patients who received at least one dose of KEYTRUDA, 38% experienced serious adverse reactions. The most frequent serious adverse reactions reported in $\geq 1\%$ of KEYTRUDA-treated patients were pneumonia (2.7%), pyrexia (2.4%), stomatitis (2.4%), acute kidney injury (2.0%), pneumonitis (1.6%), COVID-19 (1.2%), death not otherwise specified (1.2%), diarrhea (1.2%), dysphagia (1.2%), gastrostomy tube site complication (1.2%), and immune-mediated hepatitis (1.2%). Fatal adverse reactions occurred in 5% of patients, including death not otherwise specified (1.2%), acute renal failure (0.4%), hypercalcemia (0.4%), pulmonary hemorrhage (0.4%), dysphagia/malnutrition (0.4%), mesenteric thrombosis (0.4%), sepsis (0.4%), pneumonia (0.4%), COVID-19 (0.4%), respiratory failure (0.4%), cardiovascular disorder (0.4%), and gastrointestinal hemorrhage (0.4%). Permanent discontinuation of adjuvant KEYTRUDA due to an adverse reaction occurred in 17% of patients. The most frequent ($\geq 1\%$) adverse reactions that led to permanent discontinuation of adjuvant KEYTRUDA were pneumonitis, colitis, immune-mediated hepatitis, and death not otherwise specified.

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-A39, when KEYTRUDA was administered in combination with enfortumab vedotin-ejfv to patients with locally advanced or metastatic urothelial cancer (n=440), fatal adverse reactions occurred in 3.9% of patients, including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%). Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with enfortumab vedotin-ejfv; the serious adverse reactions in $\geq 2\%$ of patients were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%). Permanent discontinuation of KEYTRUDA occurred in 27% of patients. The most common adverse reactions ($\geq 2\%$) resulting in permanent discontinuation of KEYTRUDA were pneumonitis/ILD (4.8%) and rash (3.4%). The most common adverse reactions ($\geq 20\%$) occurring in patients treated with KEYTRUDA in combination with enfortumab vedotin-ejfv were rash (68%), peripheral neuropathy (67%), fatigue (51%), pruritus (41%), diarrhea (38%), alopecia (35%), weight loss (33%), decreased appetite (33%), nausea (26%), constipation (26%), dry eye (24%), dysgeusia (21%), and urinary tract infection (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-B15, the most common adverse reactions ($\geq 20\%$) occurring in cisplatin-eligible patients with MIBC treated with KEYTRUDA in combination with enfortumab vedotin-ejfv (n=403) were rash (63%), fatigue (48%),

pruritus (46%), peripheral neuropathy (43%), diarrhea (36%), alopecia (32%), decreased appetite (29%), nausea and dysgeusia (28% each), constipation (27%), urinary tract infection (UTI) and dry eye (25% each), weight loss (22%), and hyperglycemia (20%).

In the neoadjuvant phase of KEYNOTE-B15, serious adverse reactions occurred in 27% (n=403) of patients; the most frequent ($\geq 1.5\%$) were rash (3.2%), pneumonitis/interstitial lung disease (ILD) (2.2%), and diarrhea (1.7%). Fatal adverse reactions occurred in 1.7% of patients, including multiple organ dysfunction syndrome (0.5%) and COVID-19 pneumonia, cardiac arrest, pneumonia, septic shock, and urosepsis (0.2% each). Additional fatal adverse reactions were reported in 2 patients in the post-surgery phase before adjuvant treatment started, including pneumonia and sepsis (1 patient each). Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 17% of patients. The most frequent ($>1\%$) adverse reactions resulting in permanent discontinuation of KEYTRUDA were rash (2.2%), increased alanine aminotransferase (ALT) and pneumonitis/ILD (1.7% each), and hepatitis (1.2%).

Of the 403 patients in the KEYTRUDA in combination with enfortumab vedotin-ejfv arm who received neoadjuvant treatment, 13 patients (3.2%) did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery were multiple organ dysfunction syndrome (0.5%) and adenocarcinoma of colon, COVID-19 pneumonia, cardiac arrest, chronic obstructive pulmonary disease, coronary artery disease, glomerulonephritis, immune-mediated lung disease, myocarditis, pneumonia, pneumonitis, and urosepsis (0.2% each).

Of the 351 patients who received neoadjuvant treatment with KEYTRUDA in combination with enfortumab vedotin-ejfv and underwent radical cystectomy, 26 patients (7%) experienced delay of surgery (defined as time from last neoadjuvant treatment to surgery exceeding 8 weeks) due to adverse reactions.

In the adjuvant phase of KEYNOTE-B15, serious adverse reactions occurred in 35% (n=249) of patients; the most frequent ($\geq 1.5\%$) were UTI (8%), sepsis (2.8%), and diarrhea, hyperglycemia, and pneumonitis/ILD (1.6% each). Fatal adverse reactions occurred in 3.2% of patients, including death (0.8%) and cardiac arrest, duodenal ulcer perforation, acute pancreatitis, renal failure, small cell lung cancer, and toxic shock syndrome (0.4% each). Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 23% of patients; the most frequent ($>1\%$) were diarrhea and pneumonitis/ILD (2.4% each), rash (2%), and hyperglycemia and sepsis (1.2% each).

In KEYNOTE-905, the most common adverse reactions ($\geq 20\%$) occurring in cisplatin-ineligible patients with MIBC treated with KEYTRUDA in combination with enfortumab vedotin-ejfv (n=167) were rash (54%), pruritus (47%), fatigue (47%), peripheral neuropathy (39%), alopecia (35%), dysgeusia (35%), diarrhea (34%), constipation (28%), decreased appetite (28%), nausea (26%), UTI (24%), dry eye (21%), and weight loss (20%).

In the neoadjuvant phase of KEYNOTE-905, serious adverse reactions occurred in 27% (n=167) of patients; the most frequent ($\geq 2\%$) were UTI (3.6%) and hematuria (2.4%). Fatal adverse reactions occurred in 1.2% of patients, including myasthenia gravis and toxic epidermal necrolysis (0.6% each). Additional fatal adverse reactions were reported in 2.7% of patients in the post-surgery phase before adjuvant treatment started, including sepsis and intestinal obstruction (1.4% each). Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 15% of patients; the most frequent ($>1\%$) were rash (2.4%, including generalized exfoliative dermatitis) and increased ALT, increased aspartate aminotransferase, diarrhea, dysgeusia, and toxic epidermal necrolysis (1.2% each). Of the 167 patients in the KEYTRUDA in combination with enfortumab vedotin-ejfv arm who received neoadjuvant treatment, 7 patients (4.2%) did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery were acute myocardial infarction, bile duct cancer, colon cancer, respiratory distress, UTI, and two deaths due to myasthenia gravis and toxic epidermal necrolysis (0.6% each).

Of the 146 patients who received neoadjuvant treatment with KEYTRUDA in combination with enfortumab vedotin-ejfv and underwent radical cystectomy, 6 patients (4.1%) experienced delay of surgery (defined as time from last neoadjuvant treatment to surgery exceeding 8 weeks) due to adverse reactions.

In the adjuvant phase of KEYNOTE-905, serious adverse reactions occurred in 45% (n=96) of patients; the most frequent ($\geq 2\%$) were UTI (8%); acute kidney injury and pyelonephritis (5% each); urosepsis (4.2%); and hypokalemia, intestinal obstruction, and sepsis (2.1% each). Fatal adverse reactions occurred in 7% of patients, including urosepsis, intracranial hemorrhage, death, myocardial infarction, multiple organ dysfunction syndrome, and pseudomonas pneumonia (1% each). Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 29% of patients; the most frequent ($>2\%$) were diarrhea (5%), peripheral neuropathy, acute kidney injury, and pneumonitis (2% each).

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

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

In KEYNOTE-158 and KEYNOTE-164, adverse reactions occurring in patients with MSI-H or dMMR cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

In KEYNOTE-811, fatal adverse reactions occurred in 3 patients who received KEYTRUDA in combination with

trastuzumab and CAPOX (capecitabine plus oxaliplatin) or FP (5-FU plus cisplatin) and included pneumonitis in 2 patients and hepatitis in 1 patient. KEYTRUDA was discontinued due to adverse reactions in 13% of 350 patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma. Adverse reactions resulting in permanent discontinuation of KEYTRUDA in $\geq 1\%$ of patients were pneumonitis (2.0%) and pneumonia (1.1%). In the KEYTRUDA arm vs placebo, there was a difference of $\geq 5\%$ incidence between patients treated with KEYTRUDA vs standard of care for diarrhea (53% vs 47%), rash (35% vs 28%), hypothyroidism (11% vs 5%), and pneumonia (11% vs 5%).

In KEYNOTE-859, when KEYTRUDA was administered in combination with fluoropyrimidine- and platinum-containing chemotherapy, serious adverse reactions occurred in 45% of 785 patients. Serious adverse reactions in $>2\%$ of patients included pneumonia (4.1%), diarrhea (3.9%), hemorrhage (3.9%), and vomiting (2.4%). Fatal adverse reactions occurred in 8% of patients who received KEYTRUDA, including infection (2.3%) and thromboembolism (1.3%). KEYTRUDA was permanently discontinued due to adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA ($\geq 1\%$) were infections (1.8%) and diarrhea (1.0%). The most common adverse reactions (reported in $\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy were peripheral neuropathy (47%), nausea (46%), fatigue (40%), diarrhea (36%), vomiting (34%), decreased appetite (29%), abdominal pain (26%), palmar-plantar erythrodysesthesia syndrome (25%), constipation (22%), and weight loss (20%).

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

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

In KEYNOTE-A18, when KEYTRUDA was administered with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) to patients with FIGO 2014 Stage III-IVA cervical cancer, fatal adverse reactions occurred in 1.4% of 294 patients, including 1 case each (0.3%) of large intestinal perforation, urosepsis, sepsis, and vaginal hemorrhage. Serious adverse reactions occurred in 34% of patients; those $\geq 1\%$ included urinary tract infection (3.1%), urosepsis (1.4%), and sepsis (1%). KEYTRUDA was discontinued for adverse reactions in 9% of

patients. The most common adverse reaction ($\geq 1\%$) resulting in permanent discontinuation was diarrhea (1%). For patients treated with KEYTRUDA in combination with CRT, the most common adverse reactions ($\geq 10\%$) were nausea (56%), diarrhea (51%), urinary tract infection (35%), vomiting (34%), fatigue (28%), hypothyroidism (23%), constipation (20%), weight loss (19%), decreased appetite (18%), pyrexia (14%), abdominal pain and hyperthyroidism (13% each), dysuria and rash (12% each), back and pelvic pain (11% each), and COVID-19 (10%).

In KEYNOTE-826, when KEYTRUDA was administered in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab ($n=307$), to patients with persistent, recurrent, or first-line metastatic cervical cancer regardless of tumor PD-L1 expression who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent, fatal adverse reactions occurred in 4.6% of patients, including 3 cases of hemorrhage, 2 cases each of sepsis and due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection. Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab; those $\geq 3\%$ were febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), and acute kidney injury and sepsis (3.3% each).

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

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

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

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

In KEYNOTE-394, KEYTRUDA was discontinued due to adverse reactions in 13% of 299 patients with previously treated hepatocellular carcinoma. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was ascites (2.3%). The most common adverse reactions in patients receiving KEYTRUDA ($\geq 10\%$) were pyrexia (18%), rash (18%), diarrhea (16%), decreased appetite (15%), pruritus (12%), upper respiratory tract infection (11%), cough (11%), and hypothyroidism (10%).

In KEYNOTE-966, when KEYTRUDA was administered in combination with gemcitabine and cisplatin, KEYTRUDA was discontinued for adverse reactions in 15% of 529 patients with locally advanced unresectable or metastatic biliary tract cancer. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA ($\geq 1\%$) was pneumonitis (1.3%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ($\geq 2\%$) were decreased neutrophil count (18%), decreased platelet count (10%), anemia (6%), decreased white blood cell count (4%), pyrexia (3.8%), fatigue (3.0%), cholangitis (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.3%).

In KEYNOTE-017 and KEYNOTE-913, adverse reactions occurring in patients with MCC (n=105) were generally similar to those occurring in patients with melanoma or NSCLC who received KEYTRUDA as a single agent.

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

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

Permanent discontinuation of KEYTRUDA, LENVIMA, or both due to an adverse reaction occurred in 37% of patients; 29% KEYTRUDA only, 26% LENVIMA only, and 13% both. The most common adverse reactions ($\geq 2\%$) resulting in permanent discontinuation of KEYTRUDA, LENVIMA, or the combination were pneumonitis, myocardial

infarction, hepatotoxicity, acute kidney injury, rash (3% each), and diarrhea (2%).

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

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

In LITESPARK-022, when KEYTRUDA was administered in combination with WELIREG for the adjuvant treatment of renal cell carcinoma with a clear cell component (ccRCC) (n=915), serious adverse reactions occurred in 30% of patients. Serious adverse reactions in $\geq 1\%$ of patients included pneumonia (2%), hypoxia (1.9%), pneumonitis (1.6%), arrhythmia (1.5%), diarrhea (1.1%), and acute kidney injury (1.1%). Fatal adverse reactions occurred in 1.1% of patients who received KEYTRUDA in combination with WELIREG, including sepsis (0.1%).

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 23% of patients. Adverse reactions which resulted in permanent discontinuation of KEYTRUDA in $\geq 1\%$ of patients included increased alanine aminotransferase (ALT) (4.5%), increased aspartate aminotransferase (AST) (3%), pneumonitis (2.4%), diarrhea (2.4%), and rash (1.5%).

Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 29% of patients. Adverse reactions which required dosage interruption of KEYTRUDA in $\geq 2\%$ patients included anemia (3.2%), diarrhea (3%), increased ALT (3%), and increased AST (2.5%).

The most common ($\geq 25\%$) adverse reactions, including laboratory abnormalities, in patients who received KEYTRUDA in combination with WELIREG were decreased hemoglobin (95%), increased ALT (57%), fatigue (49%), increased AST (46%), decreased lymphocytes (38%), and increased alkaline phosphatase (29%).

In KEYNOTE-868, when KEYTRUDA was administered in combination with chemotherapy (paclitaxel and carboplatin) to patients with advanced or recurrent endometrial carcinoma (n=382), serious adverse reactions occurred in 35%

of patients receiving KEYTRUDA in combination with chemotherapy, compared to 19% of patients receiving placebo in combination with chemotherapy (n=377). Fatal adverse reactions occurred in 1.6% of patients receiving KEYTRUDA in combination with chemotherapy, including COVID-19 (0.5%) and cardiac arrest (0.3%). KEYTRUDA was discontinued for an adverse reaction in 14% of patients. Adverse reactions occurring in patients treated with KEYTRUDA and chemotherapy were generally similar to those observed with KEYTRUDA alone or chemotherapy alone, with the exception of rash (33% all Grades; 2.9% Grades 3-4).

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

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

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

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

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

In KEYNOTE-522, when KEYTRUDA was administered with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent (n=778) to patients with newly diagnosed, previously untreated, high-risk early-stage TNBC, fatal adverse reactions occurred in 0.9% of patients, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction. Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA; those $\geq 2\%$ were febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%). KEYTRUDA was discontinued in 20% of patients due to adverse reactions. The most common reactions ($\geq 1\%$) resulting in permanent discontinuation were increased ALT (2.7%), increased AST (1.5%), and rash

(1%). The most common adverse reactions ($\geq 20\%$) in patients receiving KEYTRUDA with chemotherapy followed by KEYTRUDA alone were fatigue (70%), nausea (67%), alopecia (61%), rash (52%), constipation (42%), diarrhea and peripheral neuropathy (41% each), stomatitis (34%), vomiting (31%), headache (30%), arthralgia (29%), pyrexia (28%), cough (26%), abdominal pain (24%), decreased appetite (23%), insomnia (21%), and myalgia (20%).

In KEYNOTE-D19, when KEYTRUDA was administered in combination with sacituzumab govitecan-hziy to patients with unresectable locally advanced or metastatic TNBC who had not been previously treated with systemic therapy for advanced disease and whose tumors express PD-L1 ($n=221$), fatal adverse reactions occurred in 3.2% of patients, including death due to unknown cause (0.9%), completed suicide, neutropenic sepsis, sepsis, pneumonia, and pulmonary embolism (0.5% each).

Serious adverse reactions occurred in 38% of patients receiving KEYTRUDA in combination with sacituzumab govitecan-hziy. Serious adverse reactions in $\geq 2\%$ of patients were febrile neutropenia (7%), neutropenia (6%), diarrhea (5%), fatigue and pneumonia (2.3% each).

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 9% of patients. The adverse reactions which resulted in permanent discontinuation of KEYTRUDA most commonly ($\geq 1\%$) were pneumonitis and rash (1.4% each).

Dosage interruptions of KEYTRUDA due to adverse reactions occurred in 67% of patients. Adverse reactions which required dosage interruption in $\geq 2\%$ of patients included neutropenia (36%), diarrhea (7%), upper respiratory tract infection (4.5%), anemia (4.1%), fatigue (4.1%), increased alanine aminotransferase (ALT) (3.2%), cough, leukopenia, nausea, pyrexia, rash, vomiting (2.7% each), and COVID-19 (2.3%).

The most common ($\geq 25\%$) adverse reactions, including laboratory abnormalities, occurring in patients treated with KEYTRUDA in combination with sacituzumab govitecan-hziy were decreased neutrophil count and decreased hemoglobin (86% each), decreased leukocyte count (84%), diarrhea (72%), nausea (68%), decreased lymphocyte count (61%), fatigue (58%), alopecia (52%), increased alkaline phosphatase and increased glucose (50% each), increased ALT (47%), constipation (41%), increased aspartate aminotransferase (40%), rash (37%), decreased potassium (35%), increased lactate dehydrogenase (34%), vomiting (29%), abdominal pain, headache, increased eosinophils (26% each), and decreased albumin (25%).

In KEYNOTE-355, when KEYTRUDA and chemotherapy (paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin) were administered to patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting ($n=596$), fatal adverse reactions occurred in 2.5% of patients, including cardio-respiratory arrest (0.7%) and septic shock (0.3%). Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with chemotherapy; the serious reactions in $\geq 2\%$

were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%). KEYTRUDA was discontinued in 11% of patients due to adverse reactions. The most common reactions resulting in permanent discontinuation ($\geq 1\%$) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). The most common adverse reactions ($\geq 20\%$) in patients receiving KEYTRUDA in combination with chemotherapy were fatigue (48%), nausea (44%), alopecia (34%), diarrhea and constipation (28% each), vomiting and rash (26% each), cough (23%), decreased appetite (21%), and headache (20%).

In KEYNOTE-B96, when KEYTRUDA in combination with paclitaxel, with or without bevacizumab, was administered to patients with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express PD-L1 (CPS ≥ 1), serious adverse reactions occurred in 54% of patients receiving KEYTRUDA and paclitaxel with or without bevacizumab. Serious adverse reactions in $\geq 2\%$ of patients were pneumonia (4.3%), urinary tract infection (3.9%), adrenal insufficiency, hyponatremia (3% each), COVID-19, decreased neutrophil count, pulmonary embolism (2.6% each), abdominal pain, anemia, colitis, diarrhea, febrile neutropenia, pyrexia, and vomiting (2.1% each).

Fatal adverse reactions occurred in 3.9% of patients receiving KEYTRUDA and paclitaxel, with or without bevacizumab, including assisted suicide (0.9%), death, intestinal perforation, sepsis, COVID-19, cardio-respiratory arrest, colitis, and embolic stroke (0.4% each).

KEYTRUDA was permanently discontinued for adverse reactions in 16% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA ($\geq 1\%$) were colitis and increased alanine aminotransferase (1.3% each). Adverse reactions leading to the interruption of KEYTRUDA occurred in 44% of patients. The most common adverse reactions leading to interruption of KEYTRUDA in $\geq 2\%$ were urinary tract infection (3.9%), adrenal insufficiency, pyrexia, pneumonitis, upper respiratory tract infection (2.6% each), neutropenia, diarrhea, and COVID-19 (2.1% each).

The most common adverse reactions ($\geq 20\%$) for patients treated with KEYTRUDA in combination with paclitaxel, with or without bevacizumab, were diarrhea (45%), fatigue (43%), nausea (41%), alopecia, peripheral neuropathy (38% each), epistaxis (31%), urinary tract infection (27%), constipation (25%), abdominal pain, decreased appetite, vomiting (24% each), hypothyroidism (21%), cough, hypertension, and rash (20% each).

For patients treated with KEYTRUDA in combination with paclitaxel and bevacizumab (N=169), decreased white blood cell count (27%), stomatitis (22%), and pyrexia (21%) were also reported as adverse reactions.

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 last dose.

Pediatric Use

In KEYNOTE-051, 173 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 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 25 months).

The safety and effectiveness of KEYTRUDA QLEX for the treatment of pediatric patients 12 years and older who weigh greater than 40 kg have been established for:

- Stage IIB, IIC, or III melanoma following complete resection
- Unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors
- Recurrent locally advanced or metastatic Merkel cell carcinoma

Use of KEYTRUDA QLEX in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies of KEYTRUDA in adults and additional pharmacokinetic and safety data for KEYTRUDA in pediatric patients 12 years and older. Pembrolizumab exposures in pediatric patients 12 years and older who weigh greater than 40 kg are predicted to be within range of those observed in adults at the same dosage.

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with melanoma (stage IIB, IIC, or III melanoma following complete resection in pediatric patients 12 and older), MCC, and MSI-H or dMMR cancer.

Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients.

The safety and effectiveness of KEYTRUDA QLEX have not been established in pediatric patients younger than 12 years of age for the treatment of melanoma, MCC, and MSI-H or dMMR cancer.

The safety and effectiveness of KEYTRUDA and KEYTRUDA QLEX have not been established in pediatric patients for other approved indications shown.

Adverse reactions that occurred at a $\geq 10\%$ higher rate in pediatric patients when compared to adults were pyrexia (33%), leukopenia (30%), vomiting (29%), neutropenia (28%), headache (25%), abdominal pain (23%), thrombocytopenia (22%), Grade 3 anemia (17%), decreased lymphocyte count (13%), and decreased white blood cell count (11%).

Geriatric Use

Of the 564 patients with locally advanced or metastatic urothelial cancer treated with KEYTRUDA in combination

with enfortumab vedotin-ejfv, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients. Patients 75 years of age or older treated with KEYTRUDA in combination with enfortumab vedotin-ejfv experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.

Of the 570 patients with MIBC treated with KEYTRUDA in combination with enfortumab vedotin-ejfv, 45% (n=259) were 65-74 years and 22% (n=125) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients. Patients 75 years of age or older treated with KEYTRUDA in combination with enfortumab vedotin-ejfv experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 3.6% in patients younger than 75 and 11% in patients 75 years or older.

Of 221 adult patients with TNBC who were treated with KEYTRUDA in combination with sacituzumab govitecan-hziy in KEYNOTE-D19, 26% of patients were 65 years and over and 5% were 75 years and older. No overall differences in effectiveness were observed between elderly patients and younger patients. There was a higher rate of serious adverse reactions in patients aged 65 years or older (48%) compared with younger adult patients (34%).

Additional Selected Indications in the U.S. for KEYTRUDA and KEYTRUDA QLEX

Melanoma

KEYTRUDA and KEYTRUDA QLEX are each indicated for the treatment of adult patients with unresectable or metastatic melanoma.

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

Non-Small Cell Lung Cancer

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

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

KEYTRUDA and KEYTRUDA QLEX, as single agents, are each indicated for the first-line treatment of adult patients with NSCLC expressing PD-L1 [tumor proportion score (TPS) $\geq 1\%$] as determined by an FDA-authorized 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 and KEYTRUDA QLEX, as single agents, are each indicated for the treatment of adult patients with metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$) as determined by an FDA-authorized 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 or KEYTRUDA QLEX.

KEYTRUDA and KEYTRUDA QLEX are each indicated for the treatment of adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA and KEYTRUDA QLEX, as single agents, are each indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.

Malignant Pleural Mesothelioma

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

Head and Neck Squamous Cell Cancer

KEYTRUDA and KEYTRUDA QLEX are each indicated for the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-authorized test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with platinum and fluorouracil (FU), for the first-line treatment of adult patients with metastatic or with unresectable, recurrent HNSCC.

KEYTRUDA and KEYTRUDA QLEX, as single agents, are each indicated for the first-line treatment of adult patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-authorized test.

KEYTRUDA and KEYTRUDA QLEX, as single agents, are each indicated for the treatment of adult patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Urothelial Cancer

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with enfortumab vedotin-ejfv, for the treatment of adult patients with locally advanced or metastatic urothelial cancer.

KEYTRUDA and KEYTRUDA QLEX, as single agents, are each indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:

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

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with enfortumab vedotin-ejfv, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment for the treatment of adult patients with muscle invasive bladder cancer (MIBC).

KEYTRUDA and KEYTRUDA QLEX, as single agents, are each indicated for the treatment of adult 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 and KEYTRUDA QLEX are each indicated for the treatment of adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-authorized test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. For this indication, KEYTRUDA also is indicated for the treatment of pediatric patients, and KEYTRUDA QLEX also is indicated for the treatment of pediatric patients 12 years and older.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA and KEYTRUDA QLEX are each indicated for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-authorized test.

Gastric Cancer

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-authorized test.

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-authorized test.

Esophageal Cancer

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

- in combination with platinum- and fluoropyrimidine-based chemotherapy for patients with tumors that express PD-L1 (CPS ≥ 1) as determined by an FDA-authorized test, or
- as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 (CPS ≥ 10) as determined by an FDA-authorized test.

Cervical Cancer

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with chemoradiotherapy (CRT), for the treatment of adult patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA).

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

KEYTRUDA and KEYTRUDA QLEX, as single agents, are each indicated for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-authorized test.

Hepatocellular Carcinoma

KEYTRUDA and KEYTRUDA QLEX are each indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen.

Biliary Tract Cancer

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with gemcitabine and cisplatin, for the treatment of adult patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

Merkel Cell Carcinoma

KEYTRUDA and KEYTRUDA QLEX are each indicated for the treatment of adult patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC). For this indication, KEYTRUDA also is indicated for the treatment of pediatric patients, and KEYTRUDA QLEX also is indicated for the treatment of pediatric patients 12 years and older.

Endometrial Carcinoma

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with carboplatin and paclitaxel, followed by KEYTRUDA or KEYTRUDA QLEX as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with LENVIMA, for the treatment of adult patients with advanced endometrial carcinoma that is pMMR or not MSI-H as determined by an FDA-authorized test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

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

Cutaneous Squamous Cell Carcinoma

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

Triple-Negative Breast Cancer

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

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with sacituzumab govitecan-hziy, for the first-line treatment of adult patients with unresectable locally advanced or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-authorized test.

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

Ovarian Cancer

KEYTRUDA and KEYTRUDA QLEX are each indicated, in combination with paclitaxel, with or without bevacizumab, for the treatment of adult patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-authorized test, and who have received 1 or 2 prior systemic treatment regimens.

About the Merck Access Program for WELIREG

At Merck, we are committed to supporting accessibility to our cancer medicines. Merck provides multiple programs to help appropriate patients who are prescribed WELIREG have access to our therapies. The Merck Access Program provides reimbursement support for patients receiving WELIREG, including information to help with out-of-pocket costs and co-pay assistance for eligible patients. More information is available by calling 855-257-3932 or visiting <https://www.merckaccessprogram-welireg.com/>.

About the Merck and Eisai strategic collaboration

In March 2018, Eisai and Merck, known as MSD outside of 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 jointly develop, manufacture and commercialize LENVIMA, both as monotherapy and in combination with Merck's anti-PD-1 therapy, KEYTRUDA, and HIF-2 α inhibitor, WELIREG.

Merck's focus on cancer

Every day, we follow the science as we work to discover innovations that can help patients, no matter what stage of cancer they have. As a leading oncology company, we are pursuing research where scientific opportunity and medical need converge, underpinned by our diverse pipeline of more than 20 novel mechanisms. With one of the largest clinical development programs across more than 25 tumor types, we strive to advance breakthrough science that will shape the future of oncology. By addressing barriers to clinical trial participation, screening and treatment, we work with urgency to reduce disparities and help ensure patients have access to high-quality cancer care. Our unwavering commitment is what will bring us closer to our goal of bringing life to more patients with cancer. For more information, visit <https://www.merck.com/research/oncology>.

About Merck

At Merck, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of research to deliver innovative health solutions that advance the prevention and treatment of diseases in people

and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe, sustainable and healthy future for all people and communities. For more information, visit www.merck.com and connect with us on **X (formerly Twitter)**, **Facebook**, **Instagram**, **YouTube** and **LinkedIn**.

Eisai's focus on cancer

Eisai positions Oncology as one of its key strategic areas, and aims to contribute to the cure of cancers through the discovery of innovative new drugs with new targets and mechanisms of action under the Deep Human Biology Learning (DHBL) drug discovery and development organization.

By utilizing biomarker data obtained from our products to elucidate the mechanisms of the incidence and root causes of cancer, as well as drug resistance, and using Eisai Group's precision chemistry technology to turn undruggable intracellular therapeutic targets into druggable ones, we will create new backbone therapeutic drugs.

About Eisai

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

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

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

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

This news release of Merck & Co., Inc., Rahway, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline candidates that the candidates will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially

from those set forth in the forward-looking statements.

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

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's Annual Report on Form 10-K for the year ended December 31, 2025 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Please see Prescribing Information, including information for the Boxed Warning about embryo-fetal toxicity, for WELIREG (belzutifan) at https://www.merck.com/product/usa/pi_circulars/w/welireg/welireg_pi.pdf and Medication Guide for WELIREG at https://www.merck.com/product/usa/pi_circulars/w/welireg/welireg_mg.pdf.

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

Please see Prescribing Information for KEYTRUDA (pembrolizumab) at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf and Medication Guide for KEYTRUDA at https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_mg.pdf.

Please see Prescribing Information for KEYTRUDA QLEX (pembrolizumab and berahyaluronidase alfa-pmph) at https://www.merck.com/product/usa/pi_circulars/k/keytruda_qlex/keytruda_qlex_pi.pdf and Medication Guide for KEYTRUDA QLEX at https://www.merck.com/product/usa/pi_circulars/k/keytruda_qlex/keytruda_qlex_mg.pdf.

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