Merck would like to inform you that KEYTRUDA® (pembrolizumab) Injection 100 mg is approved for 42 indications across 18 types of cancer.

- One indication that the FDA has now approved is KEYTRUDA 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-approved 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.

FDA = Food and Drug Administration; PD-L1 = programmed death ligand 1.

SELECTED SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

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

immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

- Withhold or permanently discontinue KEYTRUDA depending on severity of the immune-mediated adverse reaction. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose adverse reactions are not controlled with corticosteroid therapy.

Selected Safety Information continued below.

KEYNOTE-689

Neoadjuvant and Adjuvant Treatment of Locally Advanced HNSCC for Tumors Expressing PD-L1 (CPS ≥1)

The efficacy of KEYTRUDA was investigated in KEYNOTE-689, a randomized, multicenter, open-label, active-controlled trial conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC [AJCC, 8th edition]. Patients with active autoimmune disease requiring systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor stage (III vs. IVA) and PD-L1 status (TPS ≥50% vs. TPS <50%) according to the PD-L1 IHC 22C3 pharmDx kit.

Patients were randomized (1:1) to one of the following treatment arms:

- neoadjuvant KEYTRUDA 200 mg for 2 cycles prior to surgical resection. Within 6 weeks following surgery, 3 cycles of adjuvant KEYTRUDA 200 mg every 3 weeks in combination with radiotherapy (RT) with or without 3 cycles of cisplatin 100 mg/m^2 every 3 weeks. This was followed by KEYTRUDA 200 mg every 3 weeks for up to 12 cycles.
- no neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, adjuvant RT with or without 3 cycles of concurrent cisplatin 100 mg/m^2 every 3 weeks.

  On both treatment arms, patients received cisplatin with adjuvant RT if high-risk pathological features (i.e., positive margins <1 mm or extranodal extension) were present at surgery.

Treatment with KEYTRUDA continued until disease progression by RECIST v1.1 per BICR during the neoadjuvant phase that precluded surgery, local or metastatic recurrence during the adjuvant phase, completion of treatment, or unacceptable toxicity. Assessment of tumor status was performed prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed 12 weeks after end of RT with or without cisplatin treatment and then every 3 months until the end of year 3; then every 6 months thereafter up to the end of year 5.

The trial was not designed to isolate the effect of KEYTRUDA in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was event-free survival (EFS) by BICR defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant disease progression or recurrence, or death due to any cause. Additional efficacy outcome measures were major pathological response (mPR) as assessed by BIPR, and overall survival (OS).

The demographic and baseline characteristics in the 682 patients with PD-L1 expression of CPS ≥1 were: median age of 60 years (range: 22 to 87), 33% age 65 or older; 79% male; 78% White, 13% Asian and 2.5% Black or African American, 14% were Hispanic or Latino; 43% had ECOG PS of 1, and 79% were former/current smokers. Four percent of patients' tumors were HPV-positive, and 26% had Stage III disease, 74% had Stage IVA disease. Sixty-eight percent of patients' tumors had PD-L1 expression of CPS ≥10.

Eighty-eight percent of patients received definitive surgery in both the KEYTRUDA and the SOC arm.

Seventy-six percent of patients in the KEYTRUDA arm and 78% of patients in the SOC arm started the radiation phase of treatment. In the KEYTRUDA arm, 35% of patients received KEYTRUDA and cisplatin with concurrent RT, 57% of patients received KEYTRUDA alone with concurrent RT, 3% of patients received cisplatin alone with concurrent RT, 5% of patients received RT alone and one patient (0.4%) received KEYTRUDA alone without concurrent RT. On the SOC arm, 52% of patients received cisplatin with concurrent RT while 48% patients received RT alone.

The trial demonstrated a statistically significant improvement in EFS for patients randomized to the KEYTRUDA arm compared to those randomized to the SOC arm at the first pre-specified interim analysis.

Efficacy results are summarized in the table below.

Efficacy Results for KEYNOTE-689 (CPS ≥1)

Endpoint	**KEYTRUDA 200 mg every 3 weeks with RT with or without cisplatin n=347**	**RT with or without cisplatin n=335**
EFS		
Number of events, n (%)	128 (37%)	156 (47%)
Median in months* (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
Hazard ratio† (95% CI)	0.70 (0.55, 0.89)	
p-Value‡	0.00140	

* From product-limit (Kaplan-Meier) method for censored data.

†Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site and tumor stage.

‡One-sided p-value based on log-rank test stratified by primary tumor site and tumor stage. Compared to a one-sided p-value boundary of 0.0124.

AJCC = American Joint Committee on Cancer; BICR = blinded independent central review; BIPR = blinded independent pathology review; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HPV = human papillomavirus; IHC = immunohistochemistry; NR = not reached; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SOC = standard of care; TPS = tumor proportion score.

While OS results were not mature at this interim analysis, with 76% of pre-specified OS events in the CPS ≥1 population, no trend towards a detriment was observed.

Hypopharyngeal Tumors

In an exploratory subgroup analysis of patients with PD-L1-positive (CPS ≥1) hypopharyngeal tumors who were randomized (n=51), the EFS HR was 2.28 (95% CI: 0.79, 6.56). Among these patients, 23 patients in the KEYTRUDA arm received surgery, of which 17 patients (74%) had R0 resections. On the SOC arm, 23 patients received surgery, of which 20 (87%) had R0 resections.

HR = hazard ratio.

Recommended Dosage for Adult Patients With Locally Advanced HNSCC

The recommended dosage of KEYTRUDA for the treatment of patients with resectable locally advanced HNSCC is 200 mg every 3 weeks or 400 mg every 6 weeks. For neoadjuvant treatment, administer KEYTRUDA for 6 weeks until disease progression that precludes definitive surgery or unacceptable toxicity. For adjuvant treatment, administer KEYTRUDA in combination with RT with or without cisplatin. Continue KEYRUDA as a single agent. Continue KEYTRUDA until disease recurrence or unacceptable toxicity or up to one year.

Administer KEYTRUDA prior to cisplatin when given on the same day.

SELECTED SAFETY INFORMATION (*continued*)

Severe and Fatal Immune-Mediated Adverse Reactions (*continued*)

Immune-Mediated Pneumonitis

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

patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence. Pneumonitis resolved in 59% of the 94 patients.

Immune-Mediated Colitis

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

Hepatotoxicity and Immune-Mediated Hepatitis

KEYTRUDA as a Single Agent

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

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

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

Hypophysitis

- KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or

permanently discontinue KEYTRUDA depending on severity. Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (>0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) reactions. Systemic corticosteroids were required in 94% (16/17) of patients; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Thyroid Disorders

- KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity. Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). None discontinued, but KEYTRUDA was withheld in >0.1% (1) of patients.
- Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). It led to permanent discontinuation of KEYTRUDA in >0.1% (2) and withholding in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). It led to permanent discontinuation of KEYTRUDA in >0.1% (1) and withholding in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement. The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism.

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

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

Immune-Mediated Nephritis With Renal Dysfunction

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

resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

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

Other Immune-Mediated Adverse Reactions

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

Infusion-Related Reactions

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

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

- Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti–PD-1/PD-L1 treatments. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti–PD-1/PD-L1 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 its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA and advise them to use effective contraception during treatment and for 4 months after the last dose.

Adverse Reactions

- In KEYNOTE-689, the most common adverse reactions (≥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 ≥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 (≥1%) adverse reactions that led to permanent discontinuation of adjuvant KEYTRUDA were pneumonitis, colitis, immune-mediated hepatitis, and death not otherwise specified.

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.

FU = fluorouracil.

Before prescribing KEYTRUDA® (pembrolizumab), please read the Prescribing Information. The Medication Guide also is available.

For prescribers: please click here for state-required price disclosures.

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