

## KEYTRUDA(R) (pembrolizumab): Updated Indication

Public

Merck would like to inform you that the FDA has granted full approval to KEYTRUDA<sup>®</sup> (pembrolizumab) Injection 100 mg, in combination with enfortumab vedotin, and expanded the indication to:

- treatment of adult patients with locally advanced or metastatic urothelial cancer.

The combination initially received accelerated approval in April 2023 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.<sup>1</sup>

FDA=Food and Drug Administration.

### 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 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. 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-A39**

*In Combination With Enfortumab Vedotin for the Treatment of Patients With Urothelial Cancer*

- The efficacy of KEYTRUDA in combination with enfortumab vedotin was evaluated in KEYNOTE-A39, an open label, randomized, multicenter trial that enrolled 886 patients with locally advanced or metastatic urothelial cancer who received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade  $\geq 2$ , or uncontrolled diabetes defined as hemoglobin A1C (HbA1c)  $\geq 8\%$  or HbA1c  $\geq 7\%$  with associated diabetes symptoms were excluded.
- Patients were randomized 1:1 to receive either:
  - KEYTRUDA 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each

21-day cycle. KEYTRUDA was given approximately 30 minutes after enfortumab vedotin. Treatment was continued until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, KEYTRUDA was continued for up to 2 years.

- Gemcitabine 1000 mg/m<sup>2</sup> on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m<sup>2</sup> or carboplatin (AUC = 4.5 or 5) on Day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity for up to 6 cycles.
- Randomization was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.
- The median age was 69 years (range: 22 to 91); 77% were male; 67% were White, 22% were Asian, 1% were Black or African American, and 10% were unknown or other; 12% were Hispanic or Latino. Patients had a baseline ECOG performance status of 0 (49%), 1 (47%), or 2 (3%). Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 95% of patients had metastatic urothelial cancer, including 72% with visceral and 22% with liver metastases, and 5% had locally advanced urothelial cancer. Eighty-five percent of patients had urothelial carcinoma (UC) histology including 6% with UC mixed squamous differentiation and 2% with UC mixed other histologic variants. Forty-six percent of patients were considered cisplatin-ineligible and 54% were considered cisplatin-eligible at time of randomization.
- The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1. Additional efficacy outcome measures included ORR as assessed by BICR.
- The trial demonstrated statistically significant improvements in OS, PFS, and ORR for patients randomized to KEYTRUDA in combination with enfortumab vedotin as compared to platinum-based chemotherapy. Efficacy results were consistent across all stratified patient subgroups.
- The table below summarizes the efficacy results for KEYNOTE-A39.

## Efficacy Results in KEYNOTE-A39

<b>Endpoint</b>	<b>KEYTRUDA 200 mg every 3 weeks in combination with Enfortumab Vedotin n=442</b>	<b>Cisplatin or carboplatin with gemcitabine n=444</b>
<b>OS</b>		
Number (%) of patients with event	133 (30%)	226 (51%)
Median in months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)
Hazard ratio* (95% CI)	0.47 (0.38, 0.58)	
p-Value†	<0.0001	
<b>PFS</b>		
Number (%) of patients with event	223 (50%)	307 (69%)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio* (95% CI)	0.45 (0.38, 0.54)	
p-Value†	<0.0001	
<b>Confirmed Objective Response Rate‡</b>		
ORR§ % (95% CI)	68% (63, 72)	44% (40, 49)
p-Value¶	<0.0001	
Complete response	29%	12%
Partial response	39%	32%

\* Based on the stratified Cox proportional hazard regression model

† Two-sided p-Value based on stratified log-rank test

‡ Includes only patients with measurable disease at baseline (n=437 for KEYTRUDA in combination with enfortumab vedotin, n=441 for chemotherapy).

§ Based on patients with a best overall response as confirmed complete or partial response

¶ Two-sided p-Value based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases

AUC=area under the curve; BICR=blinded independent central review; CI=confidence interval; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST v1.1=Response Evaluation Criteria in Solid Tumors v1.1.

### Recommended Dosage of KEYTRUDA, When Given in Combination With Enfortumab Vedotin, for Adult Patients With Locally Advanced or Metastatic Urothelial Cancer

The recommended dose of KEYTRUDA when given in combination with enfortumab vedotin for adult patients with locally advanced or metastatic urothelial cancer is 200 mg administered after dilution as an intravenous (IV) infusion over 30 minutes every 3 weeks or 400 mg administered after dilution as an IV infusion over 30 minutes every 6 weeks until disease progression, unacceptable toxicity, or up to 24 months. KEYTRUDA should be administered after enfortumab vedotin when given on the same day. Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

### 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.

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

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

### Immune-Mediated Nephritis With Renal Dysfunction

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

### Immune-Mediated Dermatologic Adverse Reactions

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

### Other Immune-Mediated Adverse Reactions

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

### **Infusion-Related Reactions**

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

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

- Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after anti-PD-1/PD-L1 treatments. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute and chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between anti-PD-1/PD-L1 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-A39, when KEYTRUDA was administered in combination with enfortumab vedotin 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; 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 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%).

### **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.

### **Geriatric Use**

- Of the 564 patients with locally advanced or metastatic urothelial cancer treated with KEYTRUDA in combination with enfortumab vedotin, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. No overall differences in safety or 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 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.

ILD=interstitial lung disease.

**Reference: 1.** FDA supplemental accelerated approval letter BLA 125514/S-136, locally advanced or metastatic urothelial carcinoma. U.S. Food and Drug Administration. April 3, 2023. Accessed May 18, 2023. [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2023/125514Orig1s136ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2023/125514Orig1s136ltr.pdf)

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

**For prescribers: please [click here](#) for state-required price disclosures.**

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