

## **KEYTRUDA(R) (pembrolizumab): Additional Indication**

Merck would like to inform you that the FDA has approved KEYTRUDA® (pembrolizumab) for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

- MSI-H/dMMR **testing is required** prior to initiating treatment with KEYTRUDA in these patients. For the MSI-H/dMMR indication, select patients for treatment with KEYTRUDA as a single agent based on MSI-H/dMMR status in tumor specimens. An FDA-approved test for the detection of MSI-H or dMMR is not currently available.

MSI-H=microsatellite instability-high; dMMR=mismatch repair deficient.

### **SELECTED SAFETY INFORMATION for KEYTRUDA® (pembrolizumab) injection 100 mg**

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

#### **KEYNOTE-177**

The efficacy of KEYTRUDA was investigated in KEYNOTE-177 (NCT02563002), a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive KEYTRUDA 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup> (or levoleucovorin 200 mg/m<sup>2</sup>), and FU 400 mg/m<sup>2</sup> bolus on Day 1, then FU 2400 mg/m<sup>2</sup> over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m<sup>2</sup> on first infusion, then 250 mg/m<sup>2</sup> weekly.
- FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup> (or levoleucovorin 200 mg/m<sup>2</sup>), and FU 400 mg/m<sup>2</sup> bolus on Day 1, then FU 2400 mg/m<sup>2</sup> over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m<sup>2</sup> on first infusion, then 250 mg/m<sup>2</sup> weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The main efficacy outcome measures were PFS (as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) and OS. Additional efficacy outcome measures were ORR and DOR.

A total of 307 patients were enrolled and randomized to KEYTRUDA (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range: 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an ECOG PS of 0 and 48% had an ECOG PS of 1; and 27% received prior adjuvant or neoadjuvant chemotherapy. Among 154 patients randomized to receive chemotherapy, 143 received chemotherapy per the protocol. Of the 143 patients, 56% received mFOLFOX6, 44% received FOLFIRI, 70% received bevacizumab plus mFOLFOX6 or FOLFIRI, and 11% received cetuximab plus mFOLFOX6 or FOLFIRI. Among the 153 patients with MSI-H or dMMR CRC enrolled in

KEYNOTE-177 treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 11.1 months (range: 1 day to 30.6 months).

The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. At the time of the PFS analysis, the OS data were not mature (66% of the required number of events for the OS final analysis). The median follow-up time was 27.6 months (range: 0.2 to 48.3 months). The table below summarizes the key efficacy measures for KEYNOTE-177.

### Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177

Endpoint	KEYTRUDA 200 mg every 3 weeks n=153	Chemotherapy n=154
<b>PFS</b>		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value <sup>†</sup>	0.0004	
<b>Objective Response Rate<sup>‡</sup></b>		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
<b>Duration of Response<sup>§,¶</sup></b>		
Median in months (range)	NR (2.3+, 41.4+)	10.6 (2.8, 37.5+)
% with duration ≥12 months <sup>¶</sup>	75%	37%
% with duration ≥24 months <sup>¶</sup>	43%	18%

\*Based on Cox regression model

<sup>†</sup>Two-sided p-value based on log-rank test (compared to a significance level of 0.0234)

<sup>‡</sup>Based on confirmed response by BICR review

<sup>§</sup>Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm

<sup>¶</sup>Based on observed duration of response

+Denotes ongoing response

BICR=blinded independent central review; CI=confidence interval; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; FU=fluorouracil; MMR=mismatch repair; MSI=microsatellite instability; 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 for MSI-H or dMMR CRC

Please refer to the Prescribing Information for KEYTRUDA for information about dosing for MSI-H or dMMR CRC.

### SELECTED SAFETY INFORMATION (*continued*)

#### Immune-Mediated Pneumonitis

- KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%), and occurred more frequently in patients with a history of prior thoracic radiation (6.9%) compared to those without (2.9%). Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

### **Immune-Mediated Colitis**

- KEYTRUDA can cause immune-mediated colitis. Colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 2 (0.4%), 3 (1.1%), and 4 (<0.1%). Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 or greater colitis. Withhold KEYTRUDA for Grade 2 or 3; permanently discontinue KEYTRUDA for Grade 4 colitis.

### **Immune-Mediated Hepatitis**

- KEYTRUDA can cause immune-mediated hepatitis. Hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 2 (0.1%), 3 (0.4%), and 4 (<0.1%). Monitor patients for changes in liver function. Administer corticosteroids for Grade 2 or greater hepatitis and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA.

### **Immune-Mediated Endocrinopathies**

- KEYTRUDA can cause adrenal insufficiency (primary and secondary), hypophysitis, thyroid disorders, and type 1 diabetes mellitus. Adrenal insufficiency occurred in 0.8% (22/2799) of patients, including Grade 2 (0.3%), 3 (0.3%), and 4 (<0.1%). Hypophysitis occurred in 0.6% (17/2799) of patients, including Grade 2 (0.2%), 3 (0.3%), and 4 (<0.1%). Hypothyroidism occurred in 8.5% (237/2799) of patients, including Grade 2 (6.2%) and 3 (0.1%). Hyperthyroidism occurred in 3.4% (96/2799) of patients, including Grade 2 (0.8%) and 3 (0.1%), and thyroiditis occurred in 0.6% (16/2799) of patients, including Grade 2 (0.3%). Type 1 diabetes mellitus, including diabetic ketoacidosis, occurred in 0.2% (6/2799) of patients.
- Monitor patients for signs and symptoms of adrenal insufficiency, hypophysitis (including hypopituitarism), thyroid function (prior to and periodically during treatment), and hyperglycemia. For adrenal insufficiency or hypophysitis, administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for Grade 2 adrenal insufficiency or hypophysitis and withhold or discontinue KEYTRUDA for Grade 3 or Grade 4 adrenal insufficiency or hypophysitis. Administer hormone replacement for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate. Withhold or discontinue KEYTRUDA for Grade 3 or 4 hyperthyroidism. Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer antihyperglycemics in patients with severe hyperglycemia.

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

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

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

- Immune-mediated rashes, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor patients for suspected severe skin reactions and based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA.

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

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving KEYTRUDA and may also occur after discontinuation of treatment. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes.

Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume KEYTRUDA when the adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue KEYTRUDA for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction.

- The following clinically significant immune-mediated adverse reactions occurred in less than 1% (unless otherwise indicated) of 2799 patients: arthritis (1.5%), uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, hemolytic anemia, sarcoidosis, and encephalitis. In addition, myelitis and myocarditis were reported in other clinical trials, including classical Hodgkin lymphoma, and postmarketing use.
- Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment vs the risk of possible organ rejection in these patients.

### **Infusion-Related Reactions**

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

### **Complications of Allogeneic HSCT**

- Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic HSCT after treatment with KEYTRUDA. Follow patients closely for early evidence of transplant-related complications such as hyperacute graft-versus-host disease (GVHD), Grade 3 to 4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease (VOD), and other immune-mediated adverse reactions.
- In patients with a history of allogeneic HSCT, acute GVHD (including fatal GVHD) has been reported after treatment with KEYTRUDA. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after KEYTRUDA. Consider the benefit of KEYTRUDA vs the risk of GVHD in these patients.

### **Increased Mortality in Patients With Multiple Myeloma**

- In trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of these patients with a PD-1 or PD-L1 blocking antibody in this combination is not recommended outside of controlled trials.

### **Embryofetal Toxicity**

- Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. Advise women of this potential risk. In females of reproductive potential, verify pregnancy status prior to initiating KEYTRUDA and advise them to use effective contraception during treatment and for 4 months after the last dose.

### **Adverse Reactions**

- The most common adverse reactions (reported in  $\geq 20\%$  of patients) were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

### **Lactation**

- Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment and for 4 months after the final dose.

PD-1=programmed death receptor-1; PD-L1=programmed death ligand 1.

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