

KEYTRUDA(R) (pembrolizumab): Additional Indication

Merck would like to inform you that the FDA has approved KEYTRUDA® (pembrolizumab) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

- **TMB testing is required** prior to initiating treatment with KEYTRUDA in these patients.

FDA=Food and Drug Administration; TMB=tumor mutational burden.

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 HSCT. Based on the severity of the adverse reaction, KEYTRUDA should be withheld or discontinued and corticosteroids administered if appropriate. For more information regarding immune-mediated adverse reactions, please read the additional Selected Safety Information below.

KEYNOTE-158

The efficacy of KEYTRUDA was investigated in a prospectively-planned retrospective analysis of 10 cohorts (A through J) of patients with various previously treated unresectable or metastatic solid tumors with TMB-H who were enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). The trial excluded patients who previously received an anti-programmed death receptor-1 (PD-1) or other immune-modulating monoclonal antibody, or who had an autoimmune disease, or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Assessment of tumor status was performed every 9 weeks for the first 12 months and every 12 weeks thereafter.

The statistical analysis plan pre-specified ≥ 10 and ≥ 13 mut/Mb using the FoundationOne CDx assay as cutpoints to assess TMB. Testing of TMB was blinded with respect to clinical outcomes. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) in patients who received at least one dose of KEYTRUDA as assessed by Blinded Independent Central Review (BICR) according to Response Evaluation Criteria In Solid Tumors (RECIST) v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

In KEYNOTE-158, 1050 patients were included in the efficacy analysis population. TMB was analyzed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 102 (13%) had tumors identified as TMB-H, defined as TMB ≥ 10 mut/Mb. Among the 102 patients with TMB-H advanced solid tumors, the study population characteristics were: median age of 61 years (range: 27 to 80), 34% age 65 or older; 34% male; 81%

White; and 41% Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 and 58% ECOG PS of 1. Fifty-six percent of patients had at least two prior lines of therapy.

Efficacy results are summarized below.

Efficacy Results for Patients with TMB-H Cancer in KEYNOTE-158

Endpoint	KEYTRUDA 200 mg every 3 weeks	
	TMB ≥10 mut/Mb n=102*	TMB ≥13 mut/Mb n=70
Objective Response Rate		
ORR (95% CI)	29% (21, 39)	37% (26, 50)
Complete response rate	4%	3%
Partial response rate	25%	34%
Duration of Response	n=30	n=26
Median in months (range) [†]	NR (2.2+, 34.8+)	NR (2.2+, 34.8+)
% with duration ≥12 months	57%	58%
% with duration ≥24 months	50%	50%

*Median follow-up time of 11.1 months

[†]From product-limit (Kaplan-Meier) method for censored data

+Denotes ongoing response

NR=not reached; CI=confidence interval.

Response by Tumor Type (TMB ≥10 mut/Mb)

	N	Objective Response Rate		Duration of Response range (months)
		n (%)	95% CI	
Overall*	102	30 (29%)	(21%, 39%)	(2.2+, 34.8+)
Small cell lung cancer	34	10 (29%)	(15%, 47%)	(4.1, 32.5+)
Cervical cancer	16	5 (31%)	(11%, 59%)	(3.7+, 34.8+)
Endometrial cancer	15	7 (47%)	(21%, 73%)	(8.4+, 33.9+)
Anal cancer	14	1 (7%)	(0.2%, 34%)	18.8+
Vulvar cancer	12	2 (17%)	(2%, 48%)	(8.8, 11.0)
Neuroendocrine cancer	5	2 (40%)	(5%, 85%)	(2.2+, 32.6+)
Salivary cancer	3	PR, SD, PD		31.3+
Thyroid cancer	2	CR, CR		(8.2, 33.2+)

Mesothelioma cancer	1	PD	
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*No TMB-H patients were identified in the cholangiocarcinoma cohort

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease.

In an exploratory analysis in 32 patients enrolled in KEYNOTE-158 whose cancer had TMB \geq 10 mut/Mb and $<$ 13 mut/Mb, the ORR was 13% (95% CI: 4%, 29%), including two complete responses and two partial responses.

Recommended Dosage for TMB-H Cancer

Please refer to the Prescribing Information for KEYTRUDA for information about dosing for TMB-H.

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 Hematopoietic Stem Cell Transplantation (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 for KEYTRUDA (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.

Pediatric Use

- There is limited experience in pediatric patients. In a trial, 40 pediatric patients (16 children aged 2 years to younger than 12 years and 24 adolescents aged 12 years to 18 years) with various cancers, including unapproved usages, were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range 1–17 doses), with 34 patients (85%) receiving 2 doses or more. The safety profile in these pediatric patients was similar to that seen in adults; adverse reactions that occurred at a higher rate ($\geq 15\%$ difference) in these patients when compared to adults under 65 years of age were fatigue (45%), vomiting (38%), abdominal pain (28%), increased transaminases (28%), and hyponatremia (18%).

PD-L1=programmed death ligand 1.

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