HYPOTHETICAL PATIENT PROFILE:
Management of Immune-Mediated Hypothyroidism

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

Patricia[a]

62-Year-Old Female

Hypothetical patient

Diagnosed with metastatic melanoma.

Treatment was initiated with KEYTRUDA as monotherapy 200 mg Q3W.

- Baseline lab tests showed normal thyroid function.
- After 2 cycles of KEYTRUDA, follow-up showed a slightly elevated level of TSH.

As hypothyroidism was a concern, Patricia was further observed for changes in thyroid function.

- After 4 cycles of KEYTRUDA, Patricia experienced progressive fatigue and unexplained weight gain.
  - The lab tests revealed a high level of TSH (10.1 uIU/mL) and a low level of free T_4 in the blood.
- Presentation and workup were consistent with Grade 2 hypothyroidism.

	Date Collected	Test	Value	Units	Range
Baseline →	03/24/23	TSH	2.01	uIU/mL	0.45–5.33
	04/14/23	TSH	2.83	uIU/mL	0.45–5.33
Post 2 Cycles →	05/05/23	TSH	**5.62H**	uIU/mL	0.45–5.33
	05/26/23	TSH	**5.49H**	uIU/mL	0.45–5.33
Post 4 Cycles →	06/16/23	TSH	**10.1H**	uIU/mL	0.45–5.33

Representative readout of TSH testing.

[a]This is a hypothetical patient case, and individual results may vary.

H = high; Q3W = every 3 weeks; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

1. Chaker L et al. *Nat Rev Dis Primers.* 2022;8(1):30.

Tip!

Patients with hypothyroidism may present with symptoms but can often be asymptomatic; it is important to regularly monitor lab results such as TSH levels.[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 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.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 2–5, and the Prescribing Information. The Medication Guide also is available.

KEYTRUDA® (pembrolizumab) Injection 100 mg

Monitoring Immune-Mediated Hypothyroidism

Immune-mediated hypothyroidism:
Evaluate thyroid function at baseline and periodically during treatment.

Remember to ask patients to immediately report new or worsening signs and symptoms of immune-mediated endocrinopathies, which may include:

- Headaches that will not go away or unusual headaches
- Eye sensitivity to light
- Eye problems
- Rapid heartbeat
- Increased sweating
- Extreme tiredness
- Weight gain or weight loss
- Feeling more hungry or thirsty than usual
- Urinating more often than usual
- Hair loss
- Feeling cold
- Constipation
- Deepening voice
- Dizziness or fainting
- Changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

In clinical trials of KEYTRUDA across tumor types (N=2,799), hypothyroidism occurred in 8% (237) of patients, including Grade 3 (0.1%) and Grade 2 (6.2%).

Hypothyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (1) of patients and withholding of KEYTRUDA 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.

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.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1, and 3–5, and the Prescribing Information. The Medication Guide also is available.

Managing Immune-Mediated Hypothyroidism

NCI-CTCAE Grading[1,a]

Refer to PI and CTCAE for specific ARs related to hypothyroidism.

Dosage Modification Based on Prescribing Information for KEYTRUDA

Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	
Grade 2	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	
Grade 3	Severe symptoms; limiting self-care ADL; hospitalization indicated	**Initiate** hormone replacement and **withhold** until clinically stable, or **permanently discontinue** KEYTRUDA depending on severity.
Grade 4	Life-threatening consequences; urgent intervention indicated	**Initiate** hormone replacement and **withhold** until clinically stable, or **permanently discontinue** KEYTRUDA depending on severity.

[a]This information is derived from published CTCAE definitions, which evolve over time. It is only intended to inform about adverse event grading and is not to be used as guidance to treat patients on any therapy. Guidance on adverse reactions related to a specific treatment should be found in that product's prescribing information.

ADL = activities of daily living; AR = adverse reaction; NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events.

1. Common Terminology Criteria for Adverse Events (CTCAE). U.S. Department of Health and Human Services. Version 4.0. Published May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

SELECTED SAFETY INFORMATION *(continued)*

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

Immune-Mediated Endocrinopathies *(continued)*

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.

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1, 2, 4, and 5, and the Prescribing Information. The Medication Guide also is available.

Managing Immune-Mediated Hypothyroidism *(continued)*

Patricia
Hypothetical patient

Results

- Patricia's hypothyroidism was treated with thyroid replacement therapy while treatment with KEYTRUDA was continued.
- Three cycles later, her free T_4 increased to normal levels, her TSH levels were back to normal, and she had symptom improvement.
- Treatment with KEYTRUDA was continued while TSH and free T_4 levels were monitored.

This is a hypothetical patient case, and individual results may vary.

	Date Collected	Test	Value	Units	Range
Baseline →	03/24/23	TSH	2.01	uIU/mL	0.45–5.33
	04/14/23	TSH	2.83	uIU/mL	0.45–5.33
Post 2 Cycles →	05/05/23	TSH	**5.62H**	uIU/mL	0.45–5.33
	05/26/23	TSH	**5.49H**	uIU/mL	0.45–5.33
Post 4 Cycles →	06/16/23	TSH	**10.1H**	uIU/mL	0.45–5.33
	07/07/23	TSH	**8.27H**	uIU/mL	0.45–5.33
	07/28/23	TSH	**7.91H**	uIU/mL	0.45–5.33
Post 7 Cycles →	08/18/23	TSH	2.96	uIU/mL	0.45–5.33

Representative readout of TSH testing.

H = high; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

SELECTED SAFETY INFORMATION *(continued)*

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

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.

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

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1–3, and 5, and the Prescribing Information. The Medication Guide also is available.

KEYTRUDA® (pembrolizumab) Injection 100 mg

SELECTED SAFETY INFORMATION *(continued)*

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-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 (≥20%) with KEYTRUDA were fatigue (28%), diarrhea (26%), rash (24%), and nausea (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.

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

Before prescribing KEYTRUDA, please read the additional Selected Safety Information on pages 1–4, and the Prescribing Information. The Medication Guide also is available.

MERCK

Copyright © 2024 Merck & Co., Inc., Rahway, NJ, USA and its affiliates.
All rights reserved. US-KEY-08604 09/24