

Handbook for patients receiving therapy with KEYTRUDA®

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Introduction

Cancer treatment has advanced rapidly with emerging new drugs and therapeutic development.

KEYTRUDA® is a drug that acts differently from conventional cancer treatment.

To continue treatment whilst ensuring the safety of patients is essential for favorable outcomes from KEYTRUDA® therapy. It is essential to understand the potential side effects.

This handbook will provide information on KEYTRUDA®'s mode of action, treatment schedule, side effects, and cautions you need to take into account in everyday life.

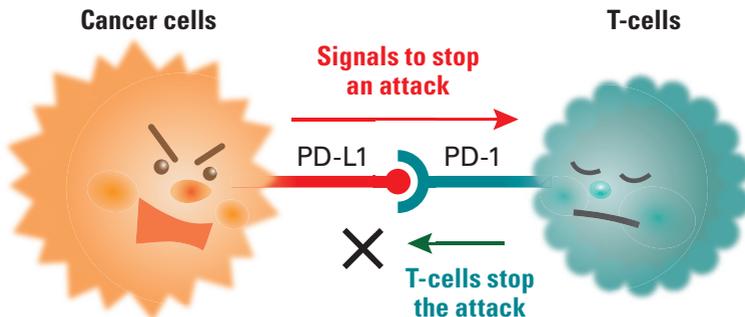


Please contact your doctors, nurses, or pharmacists if you have any questions or would like more information about the therapy with KEYTRUDA®.

How cancer cells put brakes on the immune system

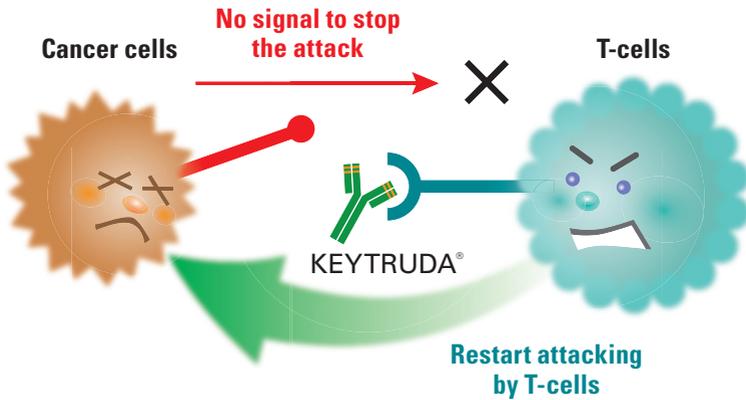
The immune response protects the body from foreign substances such as viruses or bacteria, however, the same immune system also attacks the cancer cells. Recent studies showed that cancer cells generate a signal (brake) to T-cells, which is a member of the immune system. With this brake towards the immune system, cancer cells avoid the attack from T-cells, and then the cancer cells are grown up.

PD-L1 (programmed cell death ligand 1) on the surface of cancer cells emits brake signals when it binds to PD-1 (programmed cell death protein 1) which is located on the surface of T-cells.



About KEYTRUDA®

KEYTRUDA® is an anti-PD-1 antibody classified as immune checkpoint inhibitor. KEYTRUDA® blocks the brake signals emitted from cancer cells to T-cells when it binds to PD-1 of T-cells. Then, T-cells are activated to exert anticancer activity.



Before therapy with KEYTRUDA®

- KEYTRUDA® is a drug used for cancer treatment.
- You may not be able to receive therapy with KEYTRUDA® depending on physical condition.

Patients who have experienced hypersensitivity due to ingredients containing same components of KEYTRUDA®.

Examples of hypersensitive reactions

Hypotension



Consciousness Disorder



Skin Rash



Hives



Fever



- Please inform your doctor, nurse, or pharmacist before you receive KEYTRUDA®, if you meet the following conditions.

- Have an allergy to medications or foods
- Have or had a history of autoimmune diseases*
- Have or had a history of interstitial lung disease**
- Currently under medication
- Had a history of organ transplantation or hematopoietic stem cell transplantation†
- Have or had a history of tuberculosis
- Pregnant or possibly pregnant‡

*In autoimmune disease, a person's immune system attacks the own body or tissues, though the immune response should not get aggressive to oneself. Examples are connective tissue disease such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, dermatomyositis; Crohn disease; ulcerative colitis; Graves' disease; Hashimoto disease; and type 1 diabetes.

** See page 9 regarding interstitial lung disease.

† The treatment is to replace sick hematopoietic stem cells with healthy hematopoietic stem cells. Hematopoietic stem cells develop into red blood cells, white blood cells, and platelets so that healthy blood can be produced accordingly.

‡ KEYTRUDA® may harm an unborn baby and may also cause miscarriage. In addition, female patients who wish to become pregnant should use contraception during treatment with KEYTRUDA® and for 4 months after completion of treatment.



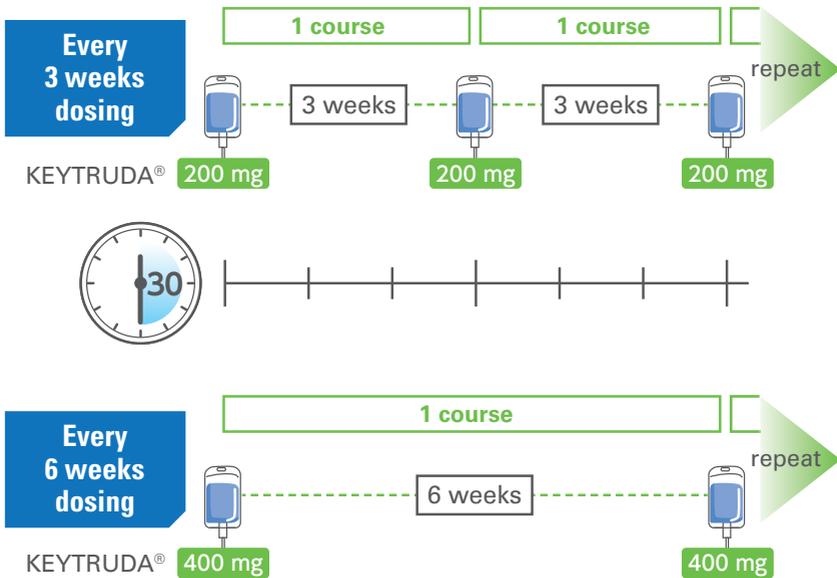
If you visit other clinical departments, please inform your doctor that you are on therapy with KEYTRUDA® by showing your KEYTRUDA® treatment diary or medication card.

Treatment schedule

KEYTRUDA® is administered as an intravenous infusion either with 200 mg every 3 weeks or 400 mg every 6 weeks for over 30 minutes.

Dosing schedule:

A single course of treatment either with 200 mg every 3 weeks or 400 mg every 6 weeks is done, and repeated depending on your disease condition.



Follow the dosage and administration schedule your doctor gives you.

Side effects should be particularly noted when

Since KEYTRUDA® activates the immune response suppressed by cancer cells, side effects may be occurred due to over work of immune system. Signs and symptoms are different for individuals. If you learn about the possible side effects, it leads you to have earlier treatments. Knowing possible side effects will lead to earlier treatment and this is also effective in preventing yourself from severe cases and long-lasting treatment. Carefully monitor the following side effects and their symptoms from KEYTRUDA® to continue your treatment without worry.

Side effects should be particularly noted when receiving KEYTRUDA®

- **Interstitial Lung Disease**
- **Colitis, Enteritis, Severe Diarrhea**
- **Severe Skin Disorder**
- **Neuropathy**
 - Guillain-Barré Syndrome, etc
- **Fulminant Hepatitis, Hepatic Failure, Liver Dysfunction, Hepatitis, Sclerosing Cholangitis**
- **Endocrine Disorder**
 - Thyroid Dysfunction
 - Pituitary Dysfunction
 - Adrenal Dysfunction
- **Type 1 Diabetes**
- **Renal Dysfunction**
- **Pancreatitis, Exocrine Pancreatic Insufficiency**
- **Myositis, Rhabdomyolysis**
- **Myasthenia Gravis**
- **Myocarditis**
- **Encephalitis, Meningitis, Myelitis**
- **Serious Blood Disorder**
 - Immune Thrombocytopenia
 - Hemolytic Anemia
 - Pure Red-cell Aplasia
 - Agranulocytosis
- **Severe Gastritis**
- **Uveitis**
- **Vasculitis**
- **Hemophagocytic Syndrome**
- **Tuberculosis**
- **Hypersensitivity Reaction to Injection** (infusion reaction)



Interstitial Lung Disease

In alveoli of the lung, carbon dioxide is exchanged with oxygen. If inflammation occurs between alveoli, the lung tissue is hardened and disturb the gas exchange. If the inflammation is spread and thickened lung tissues are increased, your breathing may be difficult. Please be careful about such life-threatening conditions.

Contact your doctor immediately

- Shortening of breathing or difficulty in breathing after climbing up stairs or slopes or when overworked
- Dry cough (cough without sputum)
- Fever

These symptoms may seem like those of common cold. When you notice those symptoms, do not assume you have just a cold. Please contact your doctor immediately.



Colitis, Enteritis, Severe Diarrhea

Inflammation may occur on the mucosa of the large or small bowel. Bleeding or severe diarrhea may be developed. Bowel perforation or ileus may result from severe inflammation process. Please be careful, sometimes symptoms are worsened and would be life-threatening.

Contact your doctor immediately

- Diarrhea (loose stools) or increased stool frequency
- Sticky stools or bloody stools
- Stabbing abdominal pain
- Nausea, vomiting
- Fever
- Fatigue, malaise

First, diarrhea may occur. Please be careful if you have four or more bowel movements a day. Treatment depends on the cause of diarrhea. Please be sure to consult your doctor for the appropriate treatment. Do not take antidiarrheal drugs at your discretion.



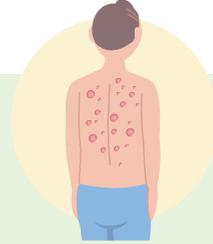
Side effects should be particularly noted when receiving KEYTRUDA®

Severe Skin Disorder

You may have red swelling over the body. Rash or blisters may occur. You may have severe canker sore, red eyelids or eyes, or fever.

Contact your doctor immediately

- Generalized erythema or blister
- Severe canker sore
- Lip erosion
- General malaise
- Red eyelids or eyes
- Fever
- Sore mucosa
- Itching



Neuropathy (e.g., Guillain-Barré Syndrome)

It begins with weakness and numbness in both hands and legs, rapidly spreading to the whole body and getting worse. You may see double or have difficulty in breathing.

Contact your doctor immediately

- Weakness of limbs
- Numbness
- Fatigue, malaise
- Difficulty in swallowing food
- Breathing difficulty
- Dizziness or headache



Fulminant Hepatitis, Hepatic Failure, Liver Dysfunction, Hepatitis, Sclerosing Cholangitis

You may hardly notice their symptoms. These are often found with abnormal laboratory values. Please be careful, sometimes symptoms are worsened, and that would be life-threatening.

Contact your doctor immediately

- **Fatigue, malaise** • **Fever**
- **Yellowing of the skin and the white of eyes (jaundice)**
- **Rash** • **Itching**
- **Appetite loss** • **Abdominal pain**
- **Nausea, vomiting** • **Abdominal bloating**

The early stage is silent, but sometimes the above symptoms indicate the presence of liver dysfunctions.



Endocrine Disorder

- Thyroid Dysfunction

Thyroid dysfunction occurs if blood thyroid hormone levels increase or decrease. The hormone is produced in the thyroid and increases the metabolism of the body. You may not be aware of these symptoms and therefore it is important for family members to pay attention.

Contact your doctor immediately

(Symptoms that may appear when thyroid hormone levels increase)

- **Weight loss despite normal eating** • **Abnormal pulse**
- **Sweating** • **Trembling of the hands and fingers**

(Symptoms that may appear when thyroid hormone levels decrease)

- **Fatigue** • **Feeling bothered** • **Constipation**
- **Weight gain despite normal eating**
- **Appetite loss** • **Slow pulse** • **Intolerance to cold**



Side effects should be particularly noted when receiving KEYTRUDA®

Endocrine Disorder

- Pituitary Dysfunction

Pituitary dysfunctions are conditions caused by too much or too little of one or more of the hormones produced by the pituitary gland. They cause various symptoms.

Contact your doctor immediately

- **Fatigue, malaise**
- **Appetite loss**



Endocrine Disorder

- Adrenal Dysfunction

The secretion of adrenal gland hormones and the level of blood glucose may decrease. Please be careful of reduced consciousness in acute cases.

Contact your doctor immediately

- **Fatigue, malaise**
- **Appetite loss**
- **Hypotension**
- **Decreased consciousness**
- **Nausea, vomiting**
- **Fever**
- **Constipation**
- **Weight loss**



Type 1 Diabetes

The pancreas does not secrete insulin, leading an increase in blood glucose chronically. Please be careful, sometimes blood glucose is rapidly increased, and that would be life-threatening.

Contact your doctor immediately

- Dry mouth or thirst
- Increased water intake
- Frequent urination
- Increased urine output
- Fatigue, malaise
- Nausea • Abdominal pain
- Decreased consciousness



Renal Dysfunction

The kidney may be inflamed, and their function is impaired. Please be careful, sometimes symptoms are worsened and would be life-threatening.

Contact your doctor immediately

- Edema
- Pain in the side or back
- Fever
- Bloody urine
- Decreased urine output
- Nausea, vomiting

Because the early stage is silent, please pay attention to the frequency of urination, urine volume, and changes in urine color.



Side effects should be particularly noted when receiving KEYTRUDA®

Pancreatitis, Exocrine Pancreatic Insufficiency

Inflammation and poor digestion may occur in the pancreas. It causes abdominal and/or back pain.

Contact your doctor immediately

- Abdominal pain
- Fatigue, malaise
- Back pain
- Yellowing of the skin and the white of eyes (jaundice)
- Oily or sour-smelling loose stools • Diarrhea
- Weight loss • Abdominal bloating

The early stage is silent, but sometimes the above symptoms indicate the presence of pancreatitis.



Myositis, Rhabdomyolysis

This disease causes inflammation in the muscle and leads to muscle weakness in the limbs and trunk.

Contact your doctor immediately

- Fatigue, malaise
- Generalized muscle stiffness
- Muscle pain
- Muscle weakness of limbs (difficulty standing up)
- Numbness of limbs
- Fever
- Reddish brown urine



Myasthenia Gravis

Patients' muscle may be weakened, and their eyelid is dropped. They might be difficult to eat food or breath.

Contact your doctor immediately

- **Fatigue, malaise**
- **Heavy eyelids**
- **Double vision**
- **Difficulty moving facial muscles**
- **Muscle weakness of limbs, shoulders, and low back**
- **Slurred speech**
- **Breathing difficulty**
- **Difficulty in swallowing**
- **Difficulty in chewing**

Symptoms differ between in the morning and in the evening



Myocarditis

Please be careful if acute cases may be life-threatening.

Contact your doctor immediately

- **Fatigue, malaise**
- **Chest pain**
- **Shortness of breath**
- **Muscle pain**
- **Edema of limbs**



Side effects should be particularly noted when receiving KEYTRUDA®

Encephalitis, Meningitis, Myelitis

You may have symptoms such as headache, vomiting, consciousness disorder, convulsion, and neck stiffness (pain in the back of the neck and difficulty in bending the neck).

Contact your doctor immediately

- Fever • Headache • Vomiting
- Stiffness in the back of the neck with difficulty in bending the neck
- Unusual behavior and language
- Decreased consciousness
- Convulsion • Weakness of limbs
- Difficulty in urinating • Constipation
- Hypoesthesia

In addition, symptoms such as difficulty seeing or limited range of vision may occur due to exacerbation of multiple sclerosis or neuromyelitis optica spectrum disorders.



Serious Blood Disorder

- Immune Thrombocytopenia

Easy or excessive bleeding may occur as a result of low levels of platelets that help to stop bleeding.

Contact your doctor immediately

- Pinpoint-like or patchy blue bruise (resistant to finger pressure)
- Bleeding from the gums or in the mouth
- Nose bleeding
- Hypermenorrhea
- Bloody urine



Serious Blood Disorder

- Hemolytic Anemia, Pure Red-cell Aplasia

Red blood cells are decreased. That impairs enough oxygen delivery throughout the body and causes anemic symptoms.

Contact your doctor immediately

- Dizziness
- Fatigue, malaise
- Palpitations, shortness of breath
- Headache
- Pale face
- Yellowing of the skin and the white of eyes (mild jaundice)



Serious Blood Disorder

- Agranulocytosis

Neutrophils that kill bacteria are severely decreased, and that may cause infection. Please be particularly careful sometimes fever occurs and would be life-threatening.

Contact your doctor immediately

- Fever
- Chills
- Sore throat



Side effects should be particularly noted when receiving KEYTRUDA®

Severe Gastritis

The stomach lining may become inflamed severely. Symptoms include nausea or epigastric pain.



Contact your doctor immediately

- Nausea, vomiting
- Epigastric pain or discomfort
- Appetite loss
- Difficulty in swallowing

Uveitis

Inflammation may occur in the eye. Contact your doctor immediately if you have an abnormal vision as below. Additionally, you may need to pay attention to Vogt-Koyanagi-Harada disease.

That causes generalized disorders such as headache, ringing in the ears, white spot, or gray hair.



Contact your doctor immediately

- Foggy vision
- Spots that look like flying insects in field of vision
- Light sensitivity
- Focus disorder



Vasculitis

This is a disease in which blood vessels become inflamed. You may have systemic symptoms such as headache, fever, fatigue, weight loss, and joint pain, as well as various other symptoms depending on the location of the blood vessels where the inflammation occurs.

Contact your doctor immediately

(Organ Symptoms)

- **Skin: Pinpoint-like or patchy blue bruises**
- **Blood vessels: Difference in blood pressure between the left and right sides**
- **Kidney: Bloody urine**
- **Lung: Hemoptum**
- **Gastrointestinal tract: Abdominal pain, bloody stools**
- **Nerve: Numbness, weakness of limbs**



Hemophagocytic Syndrome

White blood cells, red blood cells, or platelets are decreased and may lead to various symptoms. Please be careful, sometimes these symptoms are worsened and would be life-threatening.

Contact your doctor immediately

- **Fever**
- **Fatigue, malaise**
- **Convulsion**
- **Pinpoint-like or patchy bleeding in the skin**
- **Bloating of the stomach**
- **Swelling of the face**
- **Diarrhea**



Side effects should be particularly noted when receiving KEYTRUDA®

Tuberculosis

This is an infection caused by bacteria called Mycobacterium tuberculosis, and usually, flu-like symptoms such as fever or cough occur. Please be careful, sometimes these symptoms are worsened and would be life-threatening.

Contact your doctor immediately

- Cough
- Sputum, hemoptum
- Fever
- Fatigue, malaise
- Weight loss
- Night sweat



Hypersensitivity Reaction to Injection (infusion reaction)

Precautions during infusion (possible side effects during administration)

Infusion reactions such as allergy may occur during or immediately after drip-feed administration. If the following symptoms appear during or after infusion, contact your doctor, nurse, or pharmacist.

Contact your doctor immediately

- Itchy skin • Hives
- Hoarse voice • Sneezing
- Itchy throat
- Breathing difficulty
- Heart racing
- Decreased consciousness
- Dizziness or light headedness
- Hypotension



Please be careful if symptoms appear 1 to 2 hours after infusion.

Summary

Symptoms related to side effects of KEYTRUDA®

Headache	Encephalitis, meningitis, hemolytic anemia, pure red-cell aplasia, etc.
Reduced consciousness	Type 1 diabetes, encephalitis, meningitis, etc.
Abnormal vision	Uveitis
Heavy eyelids, difficulty moving facial muscles	Myasthenia gravis
Double vision	Myasthenia gravis
Dry mouth or thirst, excessive fluid intake	Type 1 diabetes
Bleeding from the gums or in the mouth	Immune thrombocytopenia, hemophagocytic syndrome
Sneezing	Hypersensitivity reaction to injection
Lip erosion	Severe skin disorder
Cough	Interstitial lung disease, tuberculosis
Sputum, hemoptum	Tuberculosis, vasculitis
Shortness of breath, breathing difficulty	Interstitial lung disease, Guillain-Barré syndrome, myasthenia gravis, hypersensitivity reaction to injection, myocarditis, hemolytic anemia, pure red-cell aplasia, etc.
Chest pain	Myocarditis
Nausea, vomiting	Colitis, enteritis, adrenal dysfunction, encephalitis, meningitis, type 1 diabetes, severe gastritis, etc.
Appetite loss	Fulminant hepatitis, hepatic failure, liver dysfunction, hepatitis, pituitary dysfunction, adrenal dysfunction, severe gastritis, etc.





Please contact your doctors, nurses, or pharmacists immediately if you have any of the listed symptoms or other changes in your physical condition that concern you.

Diarrhea	Colitis, enteritis, etc.
Sticky stools, bloody stools	Colitis, enteritis, vasculitis
Oily or sour-smelling loose stools	Exocrine pancreatic insufficiency
Constipation	Thyroid dysfunction, adrenal dysfunction, myelitis
Abdominal pain	Colitis, enteritis, pancreatitis, type 1 diabetes, sclerosing cholangitis, vasculitis
Abdominal bloating	Fulminant hepatitis, hepatic failure, exocrine pancreatic insufficiency, etc.
Frequent urination	Type 1 diabetes
Bloody urine	Renal dysfunction, immune thrombocytopenia, vasculitis
Decreased urine output, difficulty in urinating	Renal dysfunction, myelitis
Weakness of limbs	Guillain-Barré syndrome, myositis, rhabdomyolysis, myasthenia gravis, myelitis, vasculitis
Trembling of the hands and fingers	Thyroid dysfunction, etc.

Overall

Fever	Interstitial lung disease, colitis, enteritis, renal dysfunction, severe skin disorder, encephalitis, meningitis, agranulocytosis, hemophagocytic syndrome, tuberculosis, etc.
Fatigue, malaise	Colitis, enteritis, fulminant hepatitis, hepatic failure, liver dysfunction, hepatitis, thyroid dysfunction, adrenal dysfunction, tuberculosis, etc.
Jaundice	Fulminant hepatitis, hepatic failure, liver dysfunction, hepatitis, sclerosing cholangitis, pancreatitis, hemolytic anemia
Rash and other skin symptoms	Hypersensitivity reaction to injection, severe skin disorder, sclerosing cholangitis, hemophagocytic syndrome, etc.
Pinpoint-like or patchy blue bruise	Immune thrombocytopenia, vasculitis
Difference in blood pressure between the left and right sides	Vasculitis
Weight loss	Adrenal dysfunction, type 1 diabetes, tuberculosis, etc.
Weight gain	Thyroid dysfunction
Edema	Renal dysfunction, myocarditis
Convulsion	Encephalitis, meningitis, hemophagocytic syndrome
Numbness	Guillain-Barré syndrome, vasculitis

Contact information

Name of medical institution

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.....

Telephone number

.....
.....

Name of your doctor

.....
.....

Emergency contact

.....
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Treatment period

from / / to / /
month day year month day year

