

For Patients with Non-small Cell Lung Cancer: Combination Therapy with KEYTRUDA® and Chemotherapy

For patients receiving combination therapy with

KEYTRUDA® and chemotherapy

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[Your Treatment]

Treatment for non-squamous cell carcinoma

- ☐ KEYTRUDA® + Pemetrexed + Cisplatin
- ☐ KEYTRUDA® + Pemetrexed + Carboplatin

Treatment for squamous cell carcinoma

- ☐ KEYTRUDA® + Paclitaxel + Carboplatin
- ☐ KEYTRUDA® + Albumin-bound paclitaxel + Carboplatin



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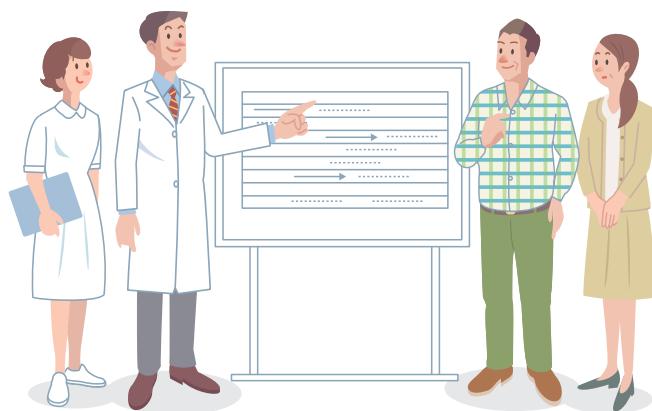
Introduction

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

KEYTRUDA® combined with chemotherapy, one of the treatment methods, attacks on cancer cells by each therapeutic action. Thus, this combination therapy is expected to have a dual therapeutic effect.

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

This book will provide information on the mode of action, treatment schedule, side effects, and cautions you need to take into account in everyday life for the combination therapy with KEYTRUDA® and chemotherapy.



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

Stage IV Non-small Cell Lung Cancer

For a patient with stage IV non-small cell lung cancer, available medications are chemotherapy with cytotoxic agents, molecular targeted agents, or immune checkpoint inhibitors including KEYTRUDA®. You are going to receive the combination therapy with KEYTRUDA® and chemotherapy.

Stages in lung cancer

Staging describes how much cancer grow or spread. There are four stages as below.

Stages I-II




Cancer locally grows nearby the lung.

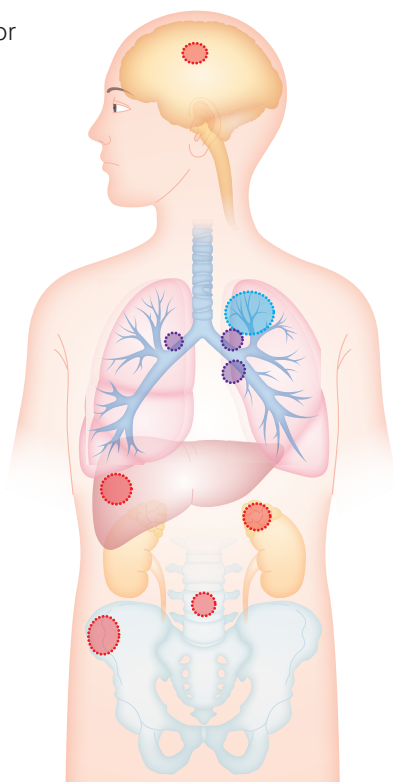
Stage III

Cancer has spread to the tissues or organs around the lung but not to other organs.

Stage IV

Cancer has spread to the organs far from the lung (distant metastasis), or with pleural fluid.

-  Primary lesion
-  Lymph node metastasis
-  Distant metastasis



Stage IV

Histology types of lung cancer

Lung cancer occurs in any tissues of the trachea, bronchus, or alveoli in the lung. It is classified into four based on the histology types: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and small cell lung cancer. Lung cancer other than small cell lung cancer (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) is called as non-small cell lung cancer. Non-small cell lung cancer other than squamous cell carcinoma is referred to as non-squamous cell carcinoma.

Histology types of lung cancer

Non-small cell lung cancer

Squamous cell carcinoma (about 20%)

Largely related to smoking.
Mainly developed in the hilum pulmonis.

Adenocarcinoma (about 60%)

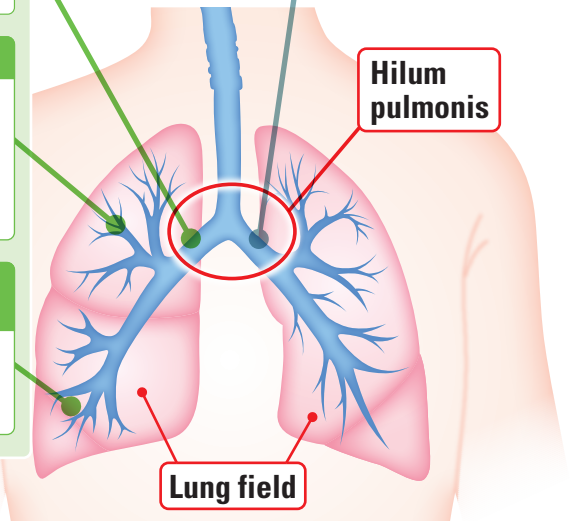
The incidence is the highest in lung cancers and has been increasing recently.
Mainly developed in the lung field.

Large cell carcinoma (about 5%)

Cancer cells are relatively large.
Mainly developed in the lung field.

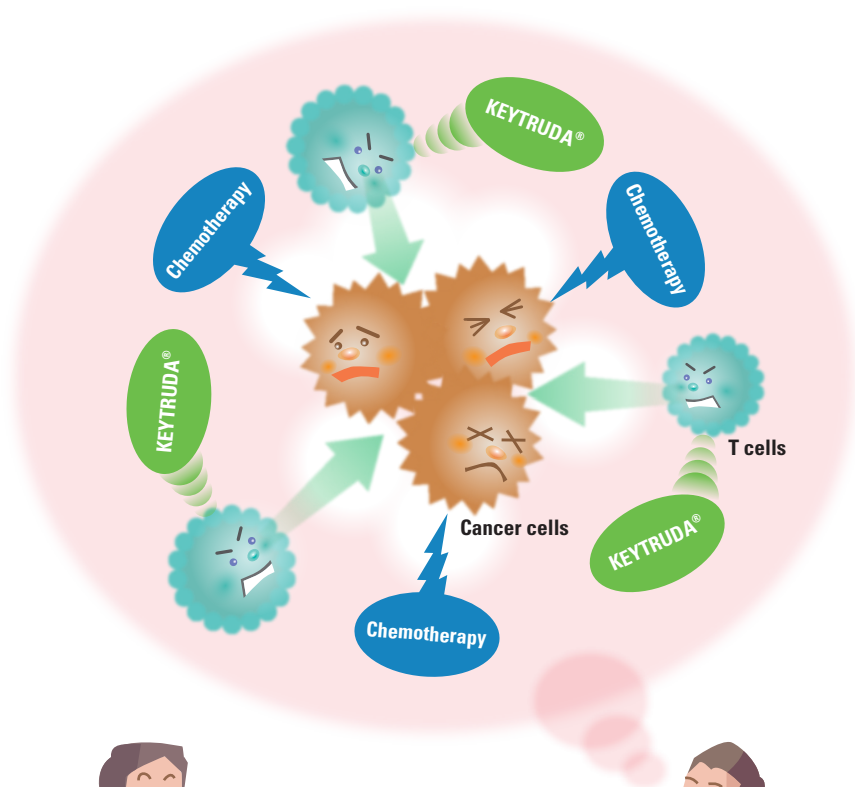
Small cell lung cancer (about 15%)

Cancer cells are relatively small.
Grow fast and tend to spread to other organs.
Mainly developed in the hilum pulmonis.



KEYTRUDA® combined with chemotherapy

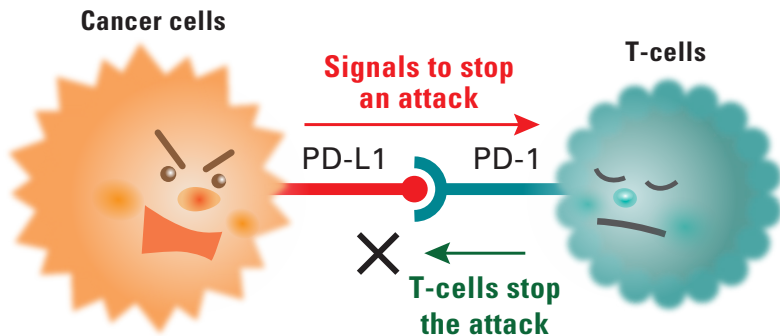
In combination therapy, KEYTRUDA® enhances the ability of T cells to kill cancer cells, and chemotherapy directly works to destroy cancer cells. These drugs act on the cells in different ways and potentially offer dual therapeutic benefits to the patients.



How cancer cells put brakes on the immune system

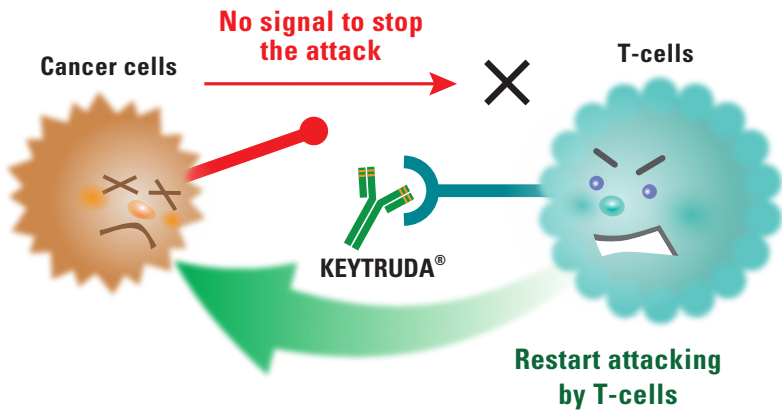
The immune response protects the body from foreign substances such as viruses or bacteria, however, the same immune system also attacks the cancer cells. Recent studies showed that cancer cells generate a signal (brake) to T-cells, which is a member of the immune system. With this brake towards the immune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



Chemotherapy

Growth of cancer cells

Healthy cells are well-controlled not to grow excessively. Abnormal cells are divided and developed repeatedly if their genes are accidentally damaged (gene mutation). We call such abnormal cells as cancer cells.

Normal cells

Growth is controlled

Cancer cells

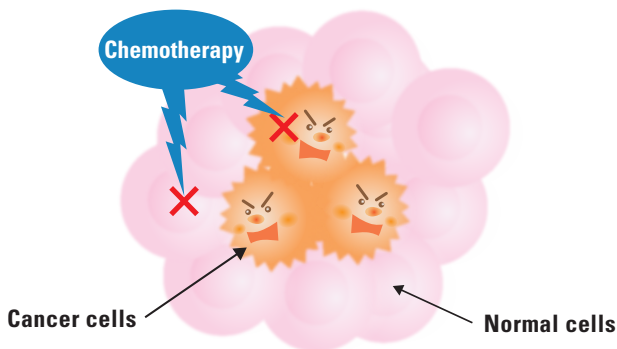
Abnormally repeated the division and growth



About chemotherapy

Chemotherapy is cytotoxic treatment. It kills cancer cells by inhibiting the growth of cells dividing abundantly.

However, it attacks not only cancer cells but also normal cells.



Cytotoxic agents used with KEYTRUDA®

Treatment for non-squamous cell carcinoma

In combination therapy for non-squamous cell carcinoma, KEYTRUDA® is used with pemetrexed and a platinum agent (cisplatin or carboplatin).

Combination of KEYTRUDA® and chemotherapy

☐ KEYTRUDA® + Pemetrexed + Cisplatin

☐ KEYTRUDA® + Pemetrexed + Carboplatin

Cytotoxic agents used with KEYTRUDA®

- Pemetrexed

Folic acid, a kind of vitamin, is essential for DNA synthesis. Cancer cells falsely intake pemetrexed, that is really like folic acid in its structure. As a result, DNA is not synthesized, causing cancer cells to die.

- Platinum agents (cisplatin and carboplatin)

A platinum agent binds to a part of DNA in cancer cells. It prevents DNA replication to kill cancer cells and suppress its growth.

In combination therapy with KEYTRUDA®, cytotoxic agents are selected based on histology types of lung cancer (non-squamous cell carcinoma or squamous cell carcinoma). Please follow your doctor's instructions for the details.



Treatment for squamous cell carcinoma

In combination therapy for squamous cell carcinoma, KEYTRUDA® is used with paclitaxel or albumin-bound paclitaxel + platinum agent (carboplatin).

Combination of KEYTRUDA® and chemotherapy

☐ KEYTRUDA® + Paclitaxel + Carboplatin

☐ KEYTRUDA® + Albumin-bound paclitaxel + Carboplatin

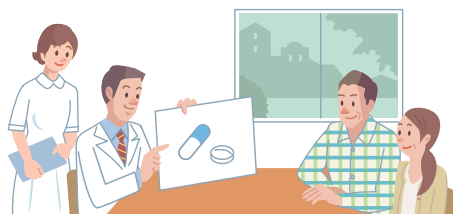
Cytotoxic agents used with KEYTRUDA®

- Paclitaxel/albumin-bound paclitaxel

These drugs interrupt cell division to suppress the growth of cancer cells.

- Platinum agent (carboplatin)

A platinum agent binds to a part of DNA in cancer cells. It affects DNA replication, kills cancer cells, and suppresses its growth.



Before combination therapy with KEYTRUDA®

Patients who may not be able to receive treatment

Patients who meet the following criteria may not be able to receive the combination therapy with KEYTRUDA® and chemotherapy.

- **Patients who have experienced hypersensitivity due to ingredients containing same components of KEYTRUDA® or cytotoxic agents.**

Examples of hypersensitive reactions

Hypotension



Consciousness Disorder



Skin Rash



Hives



Fever



- **Patients with severe bone marrow suppression**
- **Patients with infection**
- **Patients with serious renal dysfunction**
- **Pregnant or possibly pregnant patients***
- **Patients taking the following drugs if they receive the combination therapy with paclitaxel: disulfiram, cyanamide, or procarbazine hydrochloride.**

* 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.

Before you receive KEYTRUDA® combined with chemotherapy

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** or pulmonary fibrosis**
- ☐ **Have auditory disorder**
- ☐ **Have varicella**
- ☐ **Currently under medication**
- ☐ **Had a history of organ transplantation or hematopoietic stem cell transplantation†**
- ☐ **Have or had a history of tuberculosis**
- ☐ **Sensitivity to alcohol**
- ☐ **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 25 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.



In reference to the electronic package inserts of the following drugs: KEYTRUDA®, pemetrexed, cisplatin, carboplatin, paclitaxel, and albumin-bound paclitaxel.

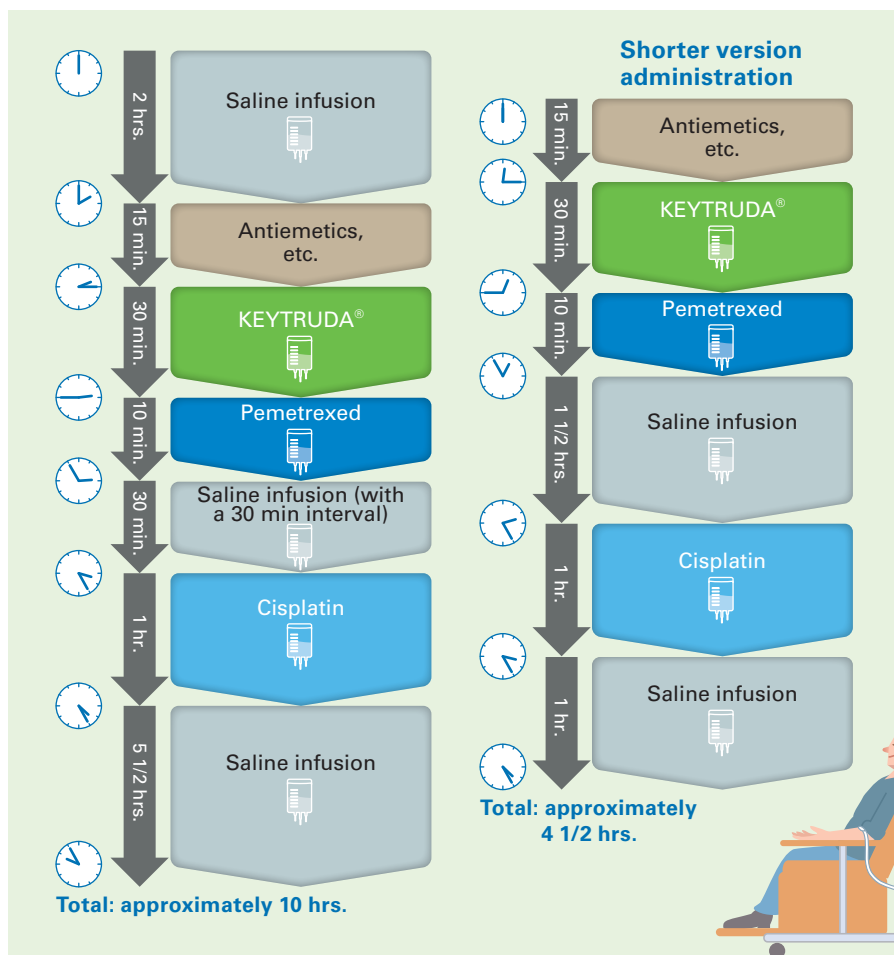
Administration schedule

● Treatment for non-squamous cell carcinoma

Example: KEYTRUDA® + Pemetrexed + Cisplatin

KEYTRUDA® 200 mg is given intravenously for approximately 30 minutes, once every 3 weeks. Then, pemetrexed is infused for approximately 10 minutes, and after approximately 30-minute interval, cisplatin is infused*. Before and after the infusion of cisplatin, saline infusion is administered.

※ When KEYTRUDA® 400 mg is given intravenously once every 6 weeks, pemetrexed and cisplatin are also given on the day without KEYTRUDA® infusion.



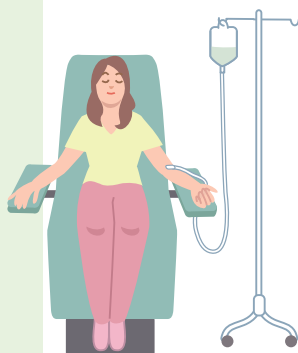
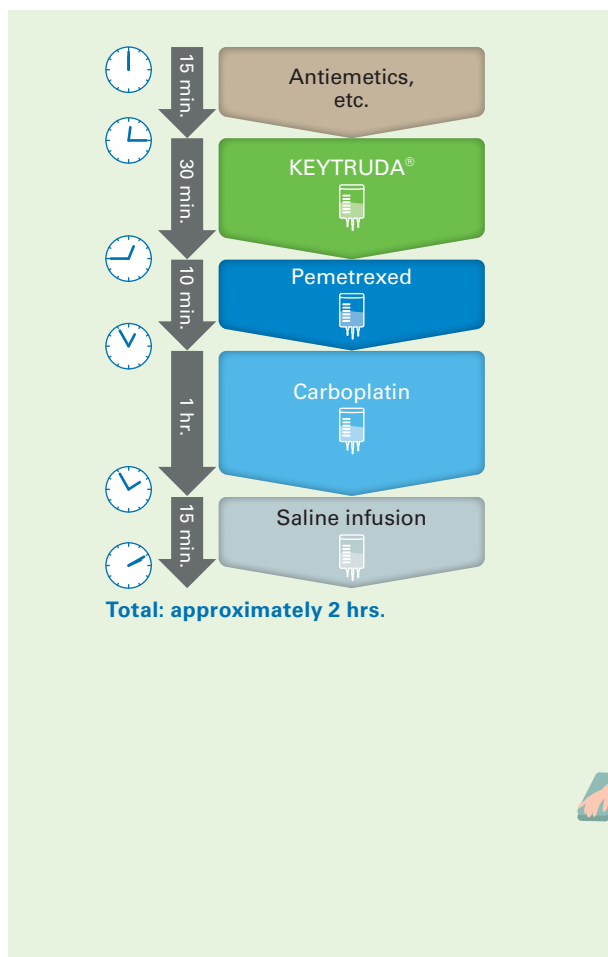
The administration schedule varies depending on the chemotherapies used with KEYTRUDA®. Please confirm your schedule.



Example: KEYTRUDA® + Pemetrexed + Carboplatin

KEYTRUDA® 200 mg is given intravenously for approximately 30 minutes, once every 3 weeks. Next, pemetrexed is infused for approximately 10 minutes, and carboplatin for approximately 1 hour*.

※ When KEYTRUDA® 400 mg is given intravenously once every 6 weeks, pemetrexed and carboplatin are also given on the day without KEYTRUDA® infusion.

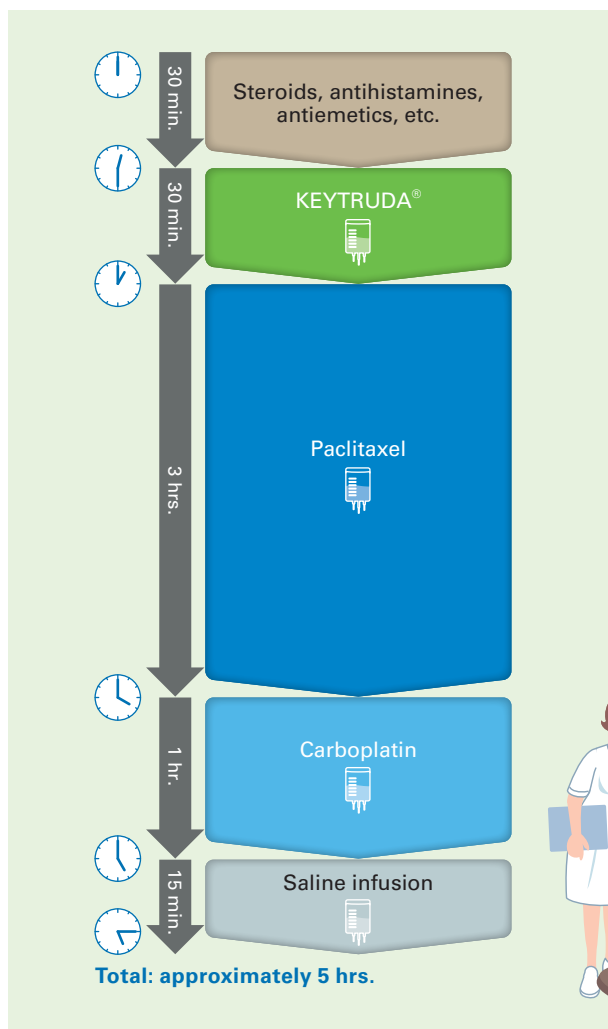


● Treatment for squamous cell carcinoma

Example: KEYTRUDA® + Paclitaxel + Carboplatin

KEYTRUDA® 200 mg is given intravenously for approximately 30 minutes, once every 3 weeks. Next, paclitaxel is infused for approximately 3 hours, and carboplatin for approximately 1 hour[※].

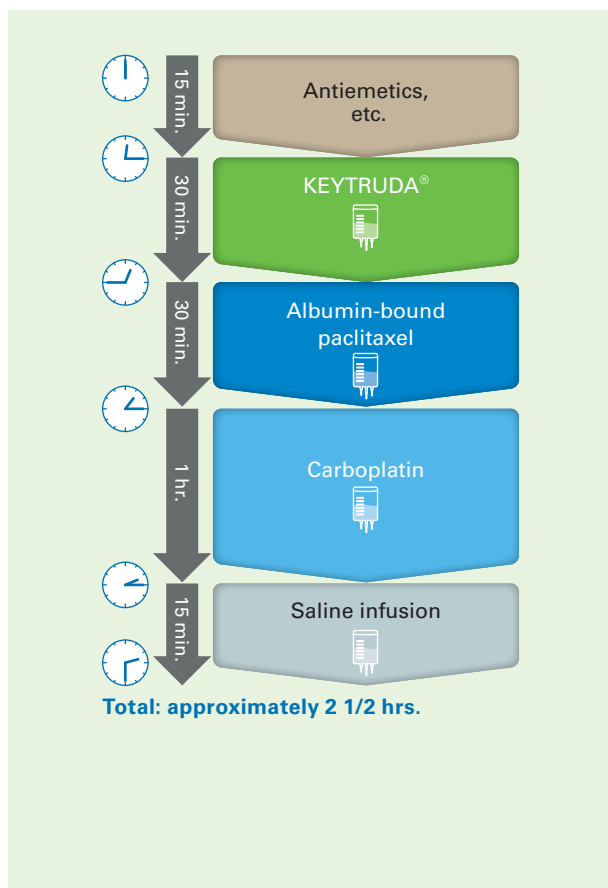
※ When KEYTRUDA® 400 mg is given intravenously once every 6 weeks, paclitaxel and carboplatin are also given on the day without KEYTRUDA® infusion.



Example: KEYTRUDA® + Albumin-bound paclitaxel + Carboplatin

KEYTRUDA® 200 mg is given intravenously for approximately 30 minutes, once every 3 weeks. On the day of treatment with KEYTRUDA®, albumin-bound paclitaxel, and carboplatin, KEYTRUDA® is given intravenously for approximately 30 minutes. Next, albumin-bound paclitaxel is infused for approximately 30 minutes, and carboplatin for approximately 1 hour in a row[※]. When a patient receives albumin-bound paclitaxel only, the infusion is for approximately 30 minutes.

※ When KEYTRUDA® 400 mg is given intravenously once every 6 weeks, albumin-bound paclitaxel and carboplatin are also given on the day without KEYTRUDA® infusion.



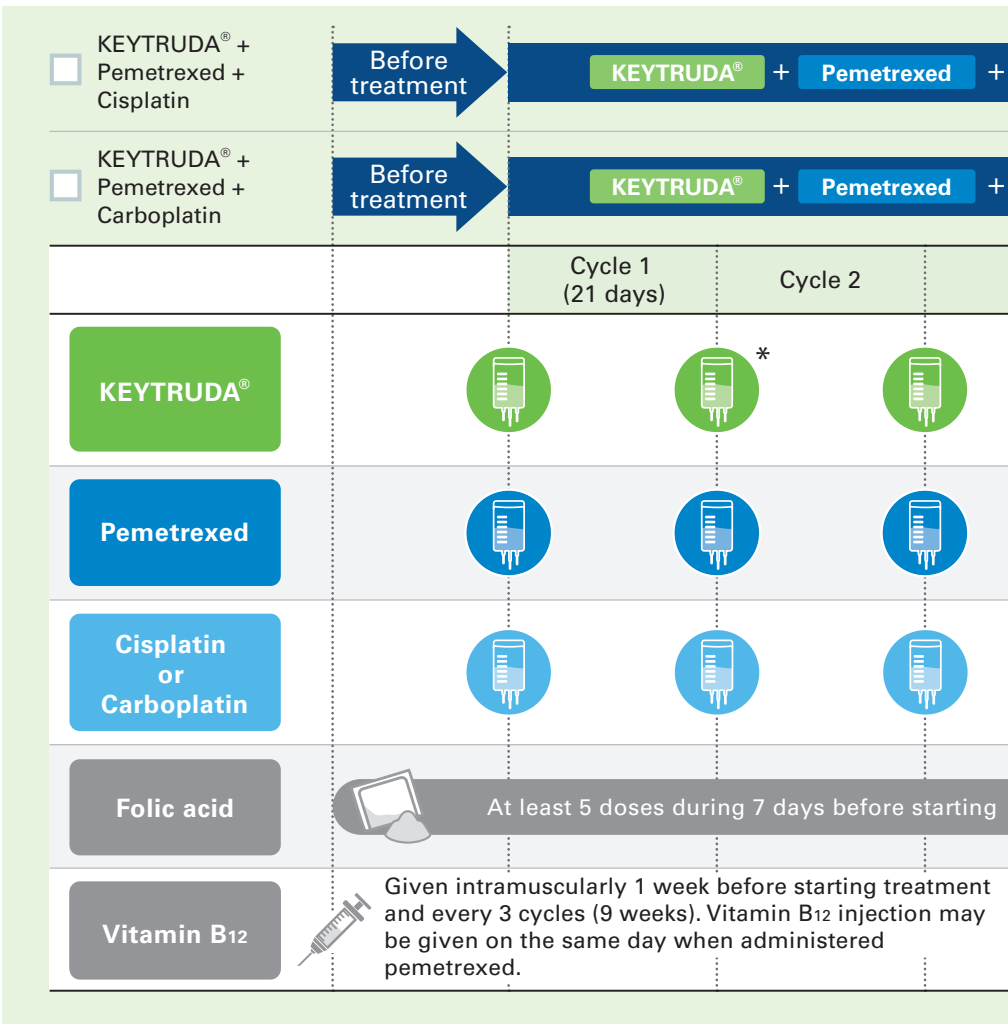
Treatment schedule

● Treatment for non-squamous cell carcinoma

KEYTRUDA® + Pemetrexed + Cisplatin/Carboplatin

KEYTRUDA® 200 mg* is given intravenously once every 3 weeks (21 days).

On Day 1, you receive KEYTRUDA®, pemetrexed, and cisplatin/carboplatin, then get the 20 days of rest. This treatment is repeated for 4 cycles.

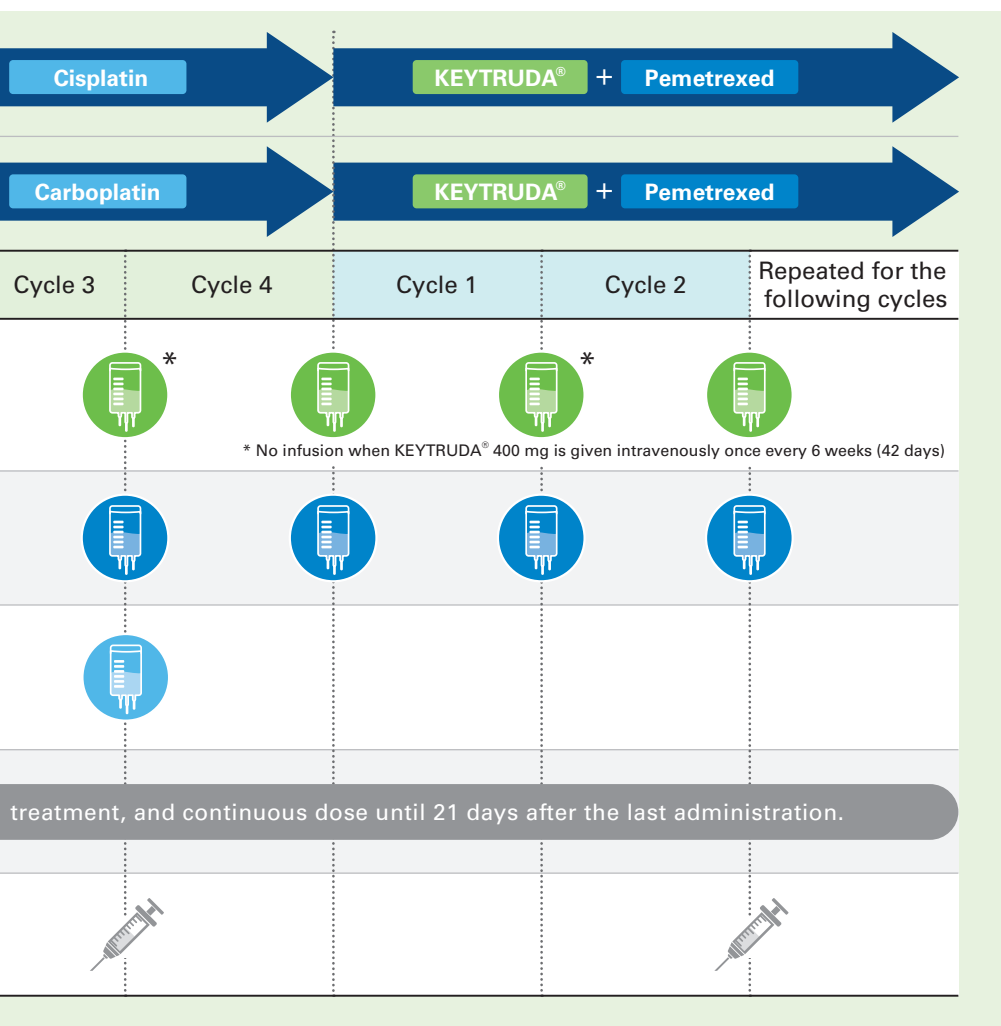


The treatment schedule varies depending on the chemotherapies used with KEYTRUDA®. Please confirm your schedule.



After the 4 cycles are completed, then you receive KEYTRUDA® 200 mg* and pemetrexed every 3 weeks. You also receive folic acid and injection of vitamin B12 to relieve side effects.

* Occasionally, KEYTRUDA® 400 mg is given intravenously once every 6 weeks (42 days), based on physician's instructions.

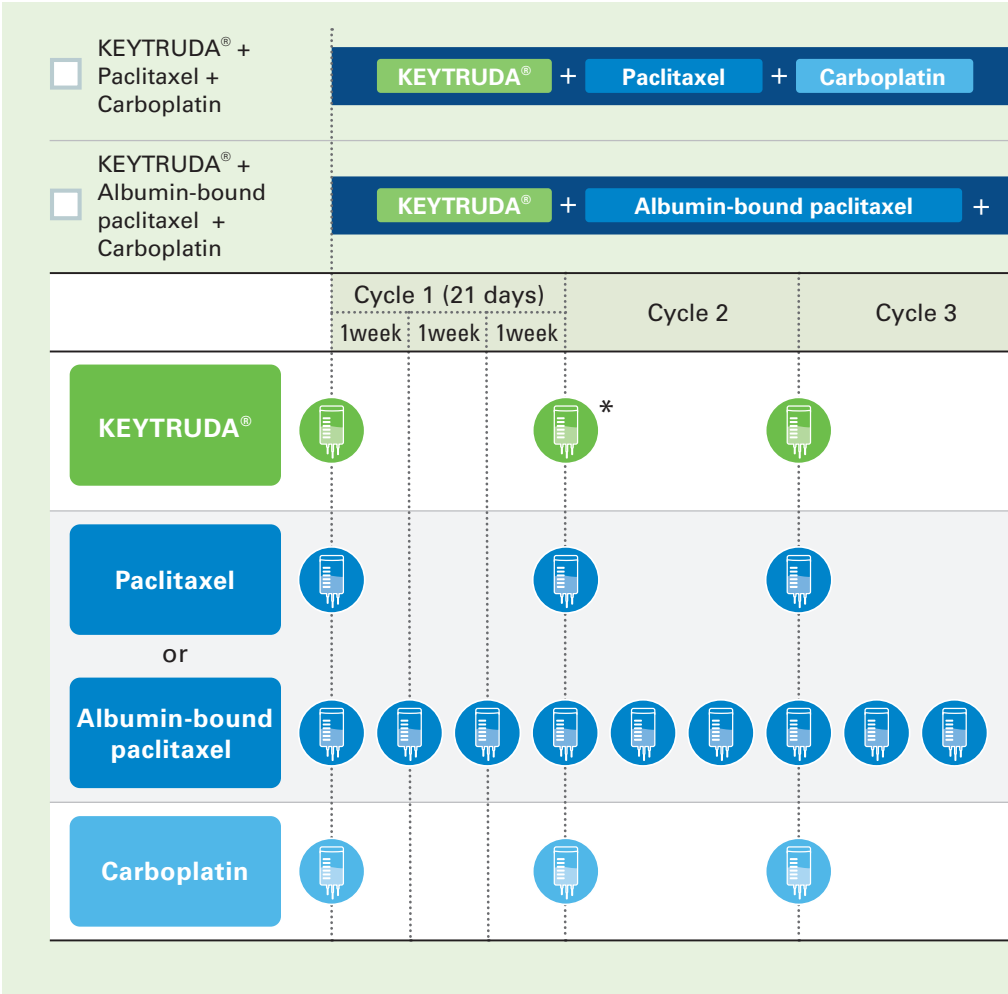


● Treatment for squamous cell carcinoma

KEYTRUDA® + Paclitaxel + Carboplatin

KEYTRUDA® 200 mg[※] is given intravenously once every 3 weeks (21 days). On Day 1, you receive KEYTRUDA®, paclitaxel, and carboplatin, then get the 20 days of rest. After the 4 cycles are completed, then you receive KEYTRUDA® 200 mg[※] every 3 weeks.

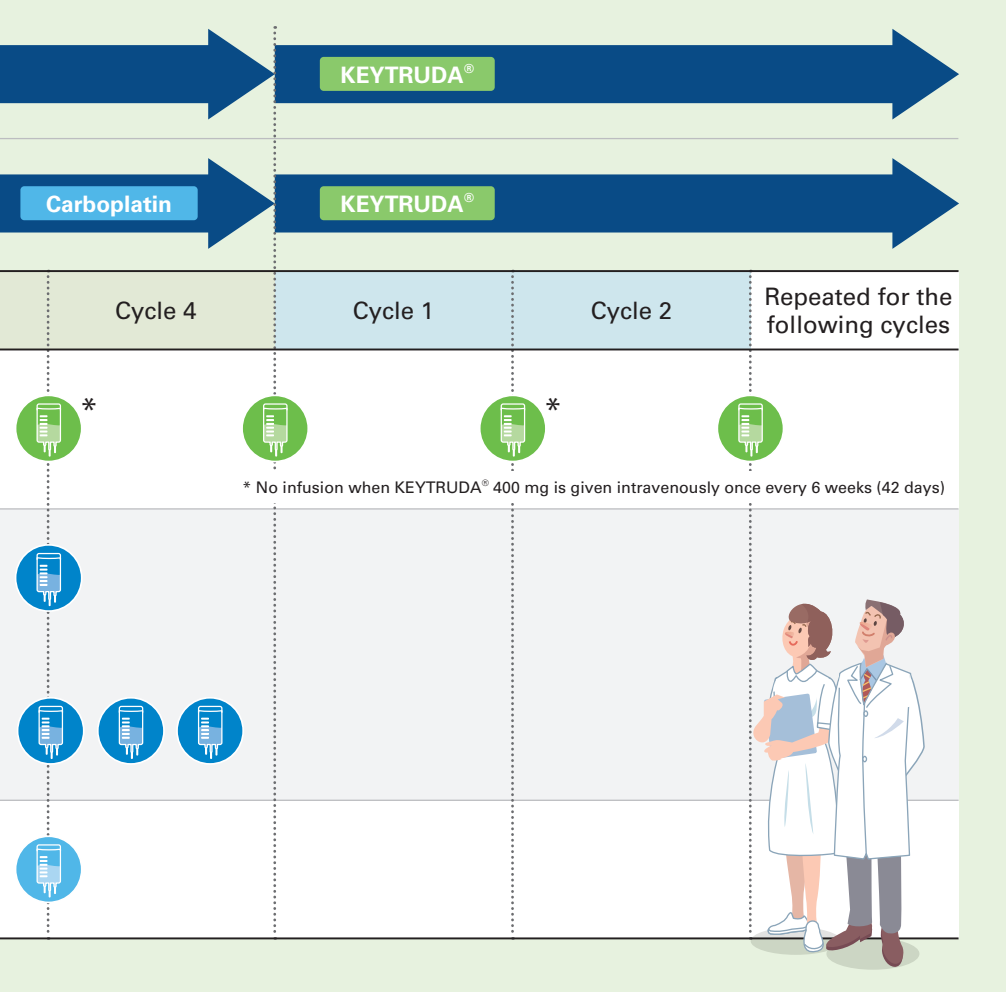
※ Occasionally, KEYTRUDA® 400 mg is given intravenously once every 6 weeks (42 days), based on physician's instructions.



KEYTRUDA® + Albumin-bound paclitaxel + Carboplatin

KEYTRUDA® 200 mg[※] is given intravenously once every 3 weeks (21 days). On Day 1, you receive KEYTRUDA®, albumin-bound paclitaxel, and carboplatin. On Day 8 and Day 15, you receive albumin-bound paclitaxel alone. After the 4 cycles are completed, then you receive KEYTRUDA® 200 mg[※] every 3 weeks.

※ Occasionally, KEYTRUDA® 400 mg is given intravenously once every 6 weeks (42 days), based on physician's instructions.



Side effects should be particularly noted in KEYTRUDA® and chemotherapy

Side effects should be particularly noted in chemotherapy

● Treatment for non-squamous cell carcinoma

Pemetrexed + **Cisplatin**

Pemetrexed + **Carboplatin**

- **Bone marrow suppression***
(e.g., Anemia or bleeding tendency)
- **Infection**
(e.g., Fever)
- **Interstitial lung disease****
(e.g., Shortness of breath, dry cough, or fever)
- **Shock, anaphylaxis**
(e.g., Respiratory distress, wheezing, hypotension, skin rash, redness, or itching)
- **Severe diarrhea**
- **Dehydration**
- **Renal failure**
- **Serious skin disorder**
- **Skin rash**
- **Nausea, vomiting**



From the Guide for appropriate use of Pemetrexed

* White blood cells, red blood cells, or neutrophils in the blood are decreased in bone marrow suppression.

** See page 25 regarding interstitial lung disease.

● Treatment for squamous cell carcinoma

Paclitaxel + **Carboplatin**

- **Sensitivity or shock**
(e.g., Respiratory distress, chest pain, hypotension, edema, hives, rash, flushing, fever, sweating, or abdominal pain)
- **Bone marrow depression***
(e.g., Anemia or bleeding tendency)
- **Peripheral neuropathy**
(e.g., Numbness of limbs, or burning pain)
- **Joint pain, muscle pain**
- **Hypotension**
- **Interstitial lung disease****
(e.g., Shortness of breath, dry cough, or fever)
- **Gastrointestinal dysfunction**
(e.g., Nausea, canker sore, or mucositis)
- **Hair loss**



From the Guide for appropriate use of Paclitaxel

Albumin-bound paclitaxel + **Carboplatin**

- **Peripheral neuropathy**
(e.g., Numbness of limbs, or burning pain)
- **Bone marrow depression***
(e.g., Anemia or bleeding tendency)
- **Infection (e.g., Fever)**
- **Cranial nerve palsy**
(e.g., Facial palsy)
- **Interstitial lung disease****
(e.g., Shortness of breath, dry cough, or fever)
- **Macular edema**



From the Guide for appropriate use of Albumin-bound paclitaxel

Side effects should be particularly noted in combination therapy with KEYTRUDA® and chemotherapy

Side effects should be particularly noted when receiving KEYTRUDA®

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 Thrombocytopenic Purpura
 - Hemolytic Anemia
 - Pure Red-cell Aplasia
 - Agranulocytosis
- **Severe Gastritis**
- **Uveitis**
- **Hemophagocytic Syndrome**
- **Tuberculosis**
- **Hypersensitivity Reaction to Injection** (infusion reaction)



Interstitial Lung Disease

In alveoli of the lung, carbon dioxide is exchanged to 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 in combination therapy with KEYTRUDA® and chemotherapy

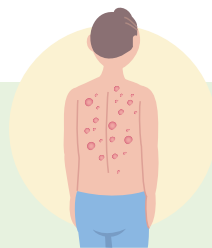
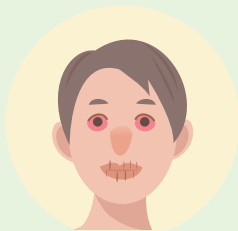
Severe Skin Disorder

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

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
- Hoarse voice • Edema
- Intolerance to cold



Side effects should be particularly noted in combination therapy with KEYTRUDA® and chemotherapy

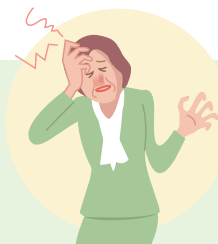
Endocrine Disorder

- 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**
- **Headache**



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**

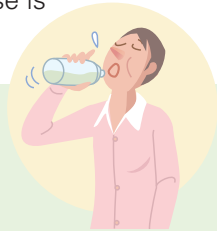


Type 1 Diabetes

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
- Diarrhea • Weight gain



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 in combination therapy with KEYTRUDA® and chemotherapy

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
- 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

This disease causes inflammation in the heart muscle with flu-like symptoms (such as fever or cough). Please be careful if acute cases may be life-threatening.

Contact your doctor immediately

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



Side effects should be particularly noted in combination therapy with KEYTRUDA® and chemotherapy

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 Thrombocytopenic Purpura

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 purpura on the skin (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 in combination therapy with KEYTRUDA® and chemotherapy

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



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



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, hemospotum
- Fever
- Fatigue, malaise
- Weight loss
- Night sweat



Side effects should be particularly noted in combination therapy with KEYTRUDA® and chemotherapy

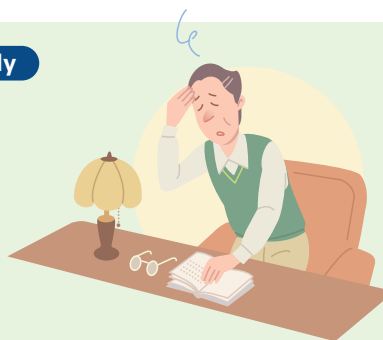
Hypersensitivity Reaction to Injection (infusion reaction)

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.

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Summary

Symptoms related to side effects of KEYTRUDA®

Headache	Pituitary dysfunction, encephalitis, meningitis, etc.
Reduced consciousness	Type 1 diabetes, encephalitis, meningitis, etc.
Abnormal vision	Uveitis
Heavy eyelids, difficulty moving facial muscles	Myasthenia gravis
Dry mouth or thirst, excessive fluid intake	Type 1 diabetes
Bleeding from the gums or in the mouth	Immune thrombocytopenic purpura, hemophagocytic syndrome
Sneezing	Hypersensitivity reaction to injection
Hoarse voice	Thyroid dysfunction, etc.
Lip erosion	Severe skin disorder
Cough	Interstitial lung disease, myocarditis, tuberculosis
Sputum, hemoptum	Tuberculosis
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
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
Abdominal bloating	Exocrine pancreatic insufficiency, etc.
Frequent urination	Type 1 diabetes
Bloody urine	Renal dysfunction, immune thrombocytopenic purpura
Decreased urine output, difficulty in urinating	Renal dysfunction, myelitis
Weakness of limbs	Guillain-Barré syndrome, myositis, rhabdomyolysis, myasthenia gravis, myelitis
Trembling of the hands and fingers	Thyroid dysfunction, etc.
Overall	
Fever	Interstitial lung disease, colitis, enteritis, renal dysfunction, severe skin disorder, myocarditis, 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, immune thrombocytopenic purpura, sclerosing cholangitis, hemophagocytic syndrome, etc.
Weight loss	Adrenal dysfunction, type 1 diabetes, tuberculosis, etc.
Weight gain	Thyroid dysfunction, renal dysfunction
Edema	Thyroid dysfunction, renal dysfunction, myocarditis
Convulsion	Encephalitis, meningitis, hemophagocytic syndrome
Numbness	Guillain-Barré syndrome

Contact information

Name of medical institution

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Telephone number

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Name of your doctor

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Emergency contact

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Treatment period

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

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