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GUIDELINES  
FOR PATIENTS®

2022

# Immunotherapy Side Effects

## Immune Checkpoint Inhibitors

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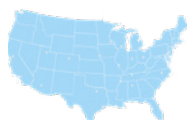


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# 1

## Immunotherapy side effects: the basics

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Immune checkpoint inhibitors (ICIs) have become the standard of care for many cancers. ICIs are a type of immunotherapy. Immunotherapy is a modern way to treat cancer. It uses the power of your own immune system to kill cancer cells.

Like all cancer treatments, immunotherapy has side effects. These side effects occur because healthy cells are being attacked by the immune system.

One job of the immune system is to recognize abnormal cells, like cancer cells. There are proteins on the surface of cancer cells. Cancer cell proteins interact with proteins on immune cells. These interactions are called immune checkpoints. PD-L1 on cancer cells interacting with PD1 on immune cells is an example. The cancer cell proteins prevent attack by “blindfolding” the immune cells. ICIs remove the blindfold. This allows the immune system to see and attack cancer cells.

Two types of currently prescribed ICIs are:

- PD-1/PD-L1 inhibitors
- The CTLA-4 inhibitor ipilimumab (Yervoy)

PD-1 and PD-L1 inhibitors include:

- Cemiplimab (Libtayo)
- Nivolumab (Opdivo)
- Pembrolizumab (Keytruda)
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Durvalumab (Imfinzi)
- Dostarlimab (Jemperli)

## Overview

Immunotherapy can cause immune cells to attack healthy cells in the body. This causes side effects. Doctors call them immune-related adverse events (irAEs). They are similar to autoimmune disorders. In these disorders the immune system sees healthy cells as a threat and attacks them.

Immunotherapy side effects range from mild to life-threatening. Most are manageable if found and treated early. Effects tend to be more severe when treatment includes both main types of ICI. Side effects can occur during or after treatment. More than one major organ may be affected. Some effects may worsen with each dose of immunotherapy.

You will be monitored for side effects and to see how treatment is working. Expect to have lab tests and physical exams on a regular basis. Tell your primary care doctor and other care providers that you are on ICI therapy.

### Which side effects are most common?

Skin reactions (rash and itching) and fatigue are very common. Many people get diarrhea and other bowel problems. Hormone-related side effects are somewhat common. Trouble breathing due to inflamed lung tissue can also occur. Effects on muscles and joints are less common. Rare but severe effects on the nervous system, kidneys, heart, and eyes are possible. See the next page for more information.

## Which side effects are most common?



**It is common to experience more than one side effect.  
Fatigue is very common and may accompany any of the side effects.**

## Treating side effects

Treating side effects is a team effort. Your care team will work with specialists in the type of side effect you are having. Some hard-to-treat reactions may require full-time treatment at a specialized care center.

### Steroids

Most side effects are treated with corticosteroids, steroids for short. These lab-made drugs act like cortisol. Cortisol is a hormone naturally made by the body. Steroids reduce the activity of the immune system. These are not the same as steroids used to build muscle mass (anabolic steroids). Steroids are not helpful for stopping or reversing some effects, including hormone-related problems.

Prednisone and methylprednisolone are the most commonly used steroids. The main difference is that methylprednisolone comes in an injectable form. This means it can be put right into the bloodstream, rather than having to take a pill.

Side effects of steroid therapy include:

- Increased appetite
- Weight gain
- Mood changes
- Retaining water
- High blood pressure

Steroids work best when started early. If you notice any new or worsening symptoms, do not wait to tell your care team.

### Stopping steroids

Steroids should not be stopped suddenly. Your care team will guide you in how to lower the dose slowly, over several weeks. This is called tapering. Stopping too quickly can cause symptoms. Withdrawal symptoms include anxiety, sweating, nausea, and trouble sleeping.

### Inflamed stomach lining

Steroids can cause the lining of the stomach to become inflamed. This is called gastritis. If you take other types of medications that also cause gastritis, you may be prescribed medication to help prevent it.

### Effect on blood sugar level

Steroids can raise blood sugar level. This is a problem for people whose blood sugar is already high due to diabetes or pre-diabetes. Blood sugar monitoring and treatment may be needed during steroid therapy.

### Effect on bone

Long-term treatment with steroids raises the risk of weak and brittle bones. This is called osteoporosis. Vitamin D and calcium can help prevent bone loss. Your doctor may also recommend physical therapy and weight-bearing exercises.

### When steroids are not enough

Sometimes treatment with steroids is not enough. Other types of medication or treatments that suppress the immune system may be needed. These are called immunosuppressants. Those most often used are described next. The choice of treatment will depend on the problem and how severe it is.

### Infliximab (Remicade)

Infliximab is a tumor necrosis factor (TNF) blocker. It blocks a protein in the immune system that worsens immune attack. Infliximab is given by IV. This means it is put into the bloodstream through a vein.

This drug can re-activate tuberculosis and the hepatitis B virus. Your blood will be tested for tuberculosis and hepatitis B and C. If you are a hepatitis carrier, you will be monitored during treatment and for a few months afterward.

### Intravenous immunoglobulin therapy (IVIg)

IVIg is an IV infusion of helpful antibodies naturally made by the immune system. The antibodies (also called immunoglobulins) come from different people.

### Mycophenolate mofetil (CellCept)

This oral medication slows down the immune system. It's used for a range of autoimmune problems. In people not on immunotherapy it is used to prevent rejection after an organ transplant.

### Rituximab (Rituxan)

B cells are a type of immune cell. They make proteins that attack your own cells by mistake. Rituximab kills B cells that have a specific marker called CD20. It is given by IV.

### Plasmapheresis

In this procedure plasma is removed from blood and replaced with plasma from a donor. Plasma is the watery, light yellow part of blood that contains antibodies and other proteins. It is also called plasma exchange.

### After a severe side effect

Immunotherapy may be paused for certain severe side effects. In some cases resuming treatment with the same ICI will not be possible. This is sometimes the case even for less severe effects.

After steroids have been slowly stopped (tapered), the affected organ(s) will be rechecked. If you have the option of resuming your ICI, you will want to make an informed decision. Discuss the benefits and harms with your doctor.

If other cancer treatment is working, it may not make sense to restart immunotherapy. The anti-cancer benefits may not be worth the risk of another severe problem.

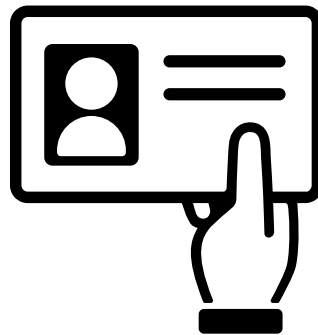
## Communication is key

Make it a point to stay in close contact with your treatment team, especially the nurses. Many side effects come on slowly. Others, such as those affecting the heart, can progress quickly. Reporting symptoms when they start can help find problems early. It also helps prevent severe complications. Symptoms that seem unrelated, like diarrhea and shortness of breath, could be signs of an irAE.

Also expect to stay in close touch with your team if you need to go on steroids. The process of slowly stopping (tapering) steroids

takes 4 to 6 weeks. During this time you will contact the nurse weekly to ask if you can make the next small decrease in dose. The dose changes will be noted in your record. This is important information that can help guide your care.

Ask your care team if there is a way to report your symptoms online. Many people find patient portals or messaging systems to be an easy way to communicate with their team.



### Immunotherapy Wallet Card

**Ask your doctor for an immunotherapy wallet card. This card states the type of immunotherapy you are receiving, potential side effects, and contact numbers for your cancer care team. Carry it with you at all times. If a card is not available, ask for a printable list of your treatment regimen. A link to a printable card is also available in the *Resources* section of this patient guide (see page 51).**



## Key points

- Immunotherapy uses the immune system to kill cancer cells.
- Immune checkpoint inhibitors (ICIs) are the most widely used type of immunotherapy.
- ICIs cause immune cells to attack healthy cells. This causes side effects called immune-related adverse events (irAEs).
- Most side effects are treated with steroids (methylprednisolone and/or prednisone).
- Side effects of steroids include increased hunger, weight gain, mood changes, retaining water, and high blood pressure.
- Steroids are stopped by slowly lowering the dose over 4 to 6 weeks. This is called tapering.
- Stopping steroids too quickly can cause anxiety, sweating, nausea, and insomnia.
- Other immune-suppressing treatments may be needed for side effects that do not improve with steroids.
- Stay in close contact with your care team. Ask for a wallet card that states your immunotherapy regimen.
- Many treatment centers provide ways to contact your team online. Ask your doctor if this is available.

# 2

## Skin

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Skin problems are common side effects of immune checkpoint inhibitor (ICI) therapy. Most are mild and can be managed without stopping immunotherapy. While rare, very serious skin reactions can occur.

Immunotherapy-related skin problems usually start in the first few weeks of treatment. If you develop symptoms such as rash, itching, or blisters, your doctor will do a complete skin exam. The goal is to find all problem areas and learn how much of the body is affected.

A full total body skin exam includes:

- The inside of the mouth
- Hair and scalp
- Fingernails and toenails

Your doctor may take pictures of the problem areas to track healing.

Blood tests are often ordered to look for signs of a severe drug reaction syndrome. It causes fever, rash, and swelling of the face and hands.

Tell your doctor about any past skin disorders. In this case seeing a dermatologist on a regular basis is recommended.

You will be asked about your symptoms and your ability to do everyday tasks. Doctors call these activities of daily living (ADLs). Basic tasks like bathing and dressing are self-care ADLs. Higher-level tasks are instrumental ADLs. Examples include food shopping, managing finances, and home maintenance.

## Activities of Daily Living (ADLs)



### Self care

- Eating
- Dressing and grooming
- Toileting
- Bathing
- Transferring



### Instrumental

- Managing finances
- Managing transportation
- Shopping and meal preparation
- Home maintenance
- Managing medications

## Rash

A rash that has both flat patches and bumps is very common during immunotherapy. Doctors call this a maculopapular rash. You may or may not have other symptoms, such as itching, burning, and tightness.

The following questions help determine if the rash is mild, moderate, or severe:

- How much of your body does the rash cover?
- Are there other symptoms, such as itching, burning, or tightness?
- Is the rash impacting your ability to do day-to-day tasks?

**Mild:** Rash covers a small area (less than 10 percent) of the body.

**Moderate:** Rash covers 10 to 30 percent of the body. It is interfering with some non-essential tasks.

**Severe:** Rash covers more than 30 percent of the body. It is interfering with basic self-care, such as bathing.

### Mild or moderate rash

You will be prescribed a steroid cream or gel. It should be applied to all areas of the rash. If the rash is itchy, taking an oral anti-histamine can help. For a moderate rash that does not improve in 1 week, your doctor may prescribe an oral steroid.

### Severe rash

In-hospital care may be needed for a severe rash. ICI therapy will be paused. A tiny piece of inflamed skin may be removed and tested (a

biopsy). Treatment with both a steroid cream or gel and an oral steroid is recommended.

## Itching

Itching (pruritis) is also common during immunotherapy. It may occur with or without a rash. The itching may be widespread or in 1 or more small areas.

The following questions help determine if the itching is mild, moderate, or severe:

- How much of your body itches?
- Is the itching constant?
- Do you have skin changes from scratching?
- Is the itching stopping you from doing everyday tasks?

**Mild:** Affects only a small area. Level of itching is not too intense.

**Moderate:** Intense or widespread itching that comes and goes. There are skin changes from picking and scratching, such as lesions, bumps, swelling, oozing, crusting, or thickening of the skin. Itching may be interfering with non-essential tasks.

**Severe:** Constant intense or widespread itching. Interferes with sleeping or basic self-care.

### Mild or moderate itching

You will be prescribed a steroid cream or gel. It should be applied to all itchy areas. An oral anti-histamine can help reduce the itching.

Gabapentin or pregabalin may be prescribed for moderate itching. These oral drugs can help relieve itching. If there is no improvement, light therapy (called narrow-band UVB phototherapy) will be considered.

### Severe itching

Immunotherapy is typically paused. Severe itching is treated with steroids and an oral anti-histamine. You may also be prescribed gabapentin or pregabalin. If there is no improvement, there are other medications your doctor may prescribe. Light therapy will also be considered for severe itching.

## Blisters

A blister is a fluid-filled sac in the outer layer of skin. Blistering is a medical emergency. This is especially true when the mouth or genitals are affected. Your doctor will consult with a skin expert (dermatologist) right away.

The contents of an unbroken blister are usually removed and tested. It is also common to have blood tests to look for specific antibodies (proteins).

The following questions help determine if the blistering is mild, moderate, or severe:

- How much of your body do the blisters cover?
- Are the blisters painful? Do you have any other symptoms?
- Are you able to do everyday tasks?

**Mild:** Blistering in one small area and no other symptoms.

**Moderate:** Blistering (possibly painful) on 10 to 30 percent of the body.

**Severe:** Blistering on more than 30 percent of body and that is preventing self-care.

**Life-threatening:** Widespread blistering and fluid problems. Requires treatment in an intensive care unit (ICU) or burn unit.

### Mild blistering

A high-strength steroid cream or gel is prescribed for mild blistering. It should be applied to all inflamed and blistered areas. Immunotherapy may be paused until all blisters have healed.

### Moderate or worse

Moderate or worse blistering is treated with steroids. If there is no improvement, your doctor may add treatment with rituximab. Intravenous immunoglobulin (IVIG) may also be given if needed for severe blistering. In-hospital care is needed for severe or life-threatening blistering. Immunotherapy will be paused.

### Stevens-Johnson syndrome (SJS)

Blistering may be a sign of this rare and serious disorder. In SJS the outer layer of skin separates from the connective tissue beneath it. If not treated it becomes a life-threatening problem called toxic epidermal necrolysis (TEN). In-hospital care and urgent treatment with steroids is needed.



## Key points

- Most skin reactions are mild and do not require stopping immunotherapy.
- Rash and itching are the most common side effects.
- If you have skin symptoms your doctor will perform a full body skin exam.
- Tell your doctor if you are having trouble doing things because of your symptoms.
- Mild or moderate rash is treated with a topical (cream or gel) steroid.
- Severe rash is treated with both an oral and a topical steroid.
- Mild or moderate itching is treated with a topical steroid and an oral anti-histamine.
- Gabapentin or pregabalin may be prescribed for moderate or severe itching.
- Light therapy may be used for moderate or severe itching that does not improve with steroids.
- Blistering is rare and serious. It could be a sign of a life-threatening skin disorder.
- A topical steroid is used for mild blistering.
- Moderate or severe blistering is treated with steroids. If there is no improvement, rituximab may be given.



**emollient**  
(eh-MOL-ee-unt)

Emollients can be found in lotions, creams, ointments, and gels. They help soothe, soften, moisturize, and protect the skin from irritation.

# 3

## Fatigue

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19 Testing

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19 Management

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21 Key points



Tiredness is common during immunotherapy. It can often be managed without stopping treatment. Severe fatigue may be a sign of a hormone-related problem. Urgent testing and treatment may be needed.

## Testing

Your doctor will want to check some things if you have fatigue. Blood tests, a physical exam, and a medication review are recommended. Blood tests ordered for fatigue are listed on the next page. See [Guide 1](#).

Tell your care team about all the medications you are taking. This includes prescription and over-the-counter drugs. Changes may be made to the types and/or doses to see if it helps.

If your doctor finds anything of concern, they will discuss it with you. Your doctor may also consult with a specialist. The evaluation helps classify fatigue as mild, moderate, or severe.

**Mild:** Improves with rest.

**Moderate:** Does not improve with rest. Interferes with certain tasks or activities.

**Severe:** Does not get better with rest. Prevents basic self-care, such as bathing.

## Management

Fatigue can be an early sign of a severe side effect. Once this has been ruled out, lifestyle changes can help with fatigue. They include:

- Staying hydrated
- Practicing good sleep habits
- Making changes to your diet

Talk to your treatment team about other ways to prevent or relieve fatigue

Immunotherapy is usually continued for mild fatigue. If it stops improving with rest, reach out to your care team.

You and your doctor will make a plan for managing moderate fatigue. Tell your treatment team if it gets worse or if you notice other health issues. Immunotherapy is sometimes paused to see if there is improvement.

Immunotherapy will be paused for severe fatigue. Your doctor will consider other possible causes. Cancer-related fatigue, other health problems, and other immunotherapy side effects can cause fatigue. Any treatable causes will be managed.

## Guide 1

## Blood tests used to evaluate fatigue

<b>Complete blood count (CBC)</b>	<ul style="list-style-type: none"> <li>• Measures the levels of red blood cells, white blood cells, and platelets</li> <li>• Can detect a range of diseases and disorders</li> <li>• Provides information on overall health</li> </ul>
<b>Comprehensive metabolic panel (CMP)</b>	<ul style="list-style-type: none"> <li>• A group of over 10 different blood tests that provide an overall picture of body chemistry and metabolism</li> </ul>
<b>TSH test</b>	<ul style="list-style-type: none"> <li>• Measures the amount of thyroid-stimulating hormone (TSH) in the blood</li> <li>• Used to learn how well the thyroid gland is working</li> </ul>
<b>Free T4 test</b>	<ul style="list-style-type: none"> <li>• Measures thyroxine (T4), one of two main hormones made by the thyroid</li> <li>• Symptoms of underactive thyroid, such as fatigue, can occur if the thyroid gland does not make enough T4</li> </ul>
<b>Cortisol test</b>	<ul style="list-style-type: none"> <li>• Measures cortisol, a hormone that helps you respond to stress, fight infection, regulate blood sugar, and other functions</li> <li>• Should be measured in the morning, when the level is at its highest</li> </ul>
<b>ACTH test</b>	<ul style="list-style-type: none"> <li>• Measures adrenocorticotropic hormone (ACTH), a hormone that stimulates the production of cortisol</li> <li>• Typically ordered if cortisol level is lower than normal</li> </ul>

## Key points

- Fatigue (tiredness) is a common side effect of immune checkpoint inhibitors.
- Severe fatigue could be a sign of a hormone problem. Urgent testing and treatment may be needed.
- Fatigue can be an early sign of a heart problem. Prompt evaluation can prevent severe complications. Hospitalization may be needed if a heart problem is found.
- Evaluating fatigue includes a physical exam, blood tests, and a medication review.
- Your doctor may make changes to your medications to see if it helps your fatigue.
- Lifestyle changes can help with fatigue. Hydration, diet changes, and practicing good sleep habits are recommended.
- Immunotherapy can be continued for mild fatigue, but may be paused for more severe fatigue.



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NCCN Guidelines for Patients  
better for everyone!**

[NCCN.org/patients/comments](https://www.nccn.org/patients/comments)



# 4

## Bowel and liver

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24 Hepatitis

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25 Key points



Immune checkpoint inhibitors (ICIs) often cause diarrhea and other bowel-related problems. Symptoms typically start in the first 6 to 8 weeks of treatment. The liver can also become inflamed, but this does not typically cause symptoms.

## Diarrhea and inflamed bowel

Diarrhea is having more bowel movements than usual, which may be watery. The lining of the large bowel (the colon) can become inflamed. This is called colitis. Colitis symptoms are listed in [Guide 2](#).

Below are examples of mild, moderate, and severe symptoms.

**Mild symptoms:** 1 to 3 bowel movements above normal per day and no colitis symptoms.

**Moderate symptoms:** 4 to 6 bowel movements above normal per day with colitis symptoms.

**Severe symptoms:** more than 6 bowel movements above normal per day with colitis symptoms. Symptoms are affecting day-to-day tasks.

Everyone's starting ("baseline") bowel habits are different. When considering symptoms, it is often the change in habits that is most helpful. For example, for those with chronic constipation or constipation due to opioid painkillers, colitis may mean 1 daily bowel movement and abdominal cramping. It is good to know your baseline bowel habits.

### Guide 2 Colitis symptoms

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Watery diarrhea

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Cramping

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Urgency

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Abdominal pain

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Blood (if severe)

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Mucus in the stool

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Fever

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Nighttime bowel movements

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### Testing

Your doctor may order stool (feces) testing. The goal is to rule out infection as the cause of your symptoms. Testing will look for bacteria, viruses, and in some cases parasites. Stool may also be tested for lactoferrin and calprotectin. These are proteins found in stool when the bowel is inflamed.

For moderate or severe symptoms, testing may include computed tomography (CT) of the abdomen and pelvis. Procedures to see inside the bowel, esophagus, and stomach are sometimes needed.

### Mild symptoms

Anti-diarrheal medications can help with mild symptoms. Try to stay hydrated and drink lots of fluids. If there is no improvement, your doctor may order stool testing. Treatment with mesalamine and/or cholestyramine may be added. Cholestyramine is most often used to lower cholesterol but can also relieve diarrhea.

Mesalamine is an anti-inflammatory drug taken by mouth.

Making changes to your diet can help. Try to avoid foods with lactose. A BRAT diet may help make stools firmer and less frequent. BRAT stands for bananas, rice, apple sauce, toast.

### **Moderate or severe symptoms**

Moderate or severe symptoms are treated with steroids. Immunotherapy is usually paused. If there is no improvement, an infusion of infliximab (Remicade) or vedolizumab (Entyvio) may be given. You may receive up to 2 more doses. See page 10 for more information on infliximab. If still needed, other immune-suppressing drugs will be considered.

You may have testing to track healing. It helps determine how long treatment is needed. Testing may include endoscopy. Endoscopy allows your doctor to see inside the colon and rectum using a lighted tube. Your stool may also be tested for lactoferrin and calprotectin.

## Hepatitis

The liver is a large organ located on the right side of the body, under the rib cage. It filters blood and helps digest foods by making a substance called bile.

Immunotherapy can cause the liver to become inflamed. This is called hepatitis. It does not typically cause symptoms. The levels of substances (enzymes) made by the liver will be checked using blood tests. High levels may be a sign that the liver is inflamed or damaged.

Some drugs can damage the liver. Taking too much acetaminophen (Tylenol), for example, can cause liver injury. Certain dietary supplements and alcohol use can also damage the liver. Your doctor will review all of your medications and supplements. Use of drugs that may harm the liver will be avoided or limited. Others will be adjusted based on how well your liver is working.

If liver enzyme levels get too high, treatment with steroids is needed. Immunotherapy may be paused. If there is no improvement, mycophenolate mofetil may be added. It is an immune-suppressing drug.

Bilirubin is a yellow substance in blood. Liver problems can cause it to build up in blood. If bilirubin and liver enzyme levels are very high, liver failure could occur. In-hospital care is needed.

## Key points

- Diarrhea and inflamed bowel (colitis) are common side effects of immunotherapy.
- Diarrhea is an increase in bowel movements, which may be watery.
- Symptoms of inflamed bowel include watery diarrhea, cramping, urgency, and pain.
- Anti-diarrheal medication and staying hydrated can help relieve mild symptoms.
- Mesalamine or cholestyramine may be added if mild symptoms do not improve.
- Avoiding lactose and starting a BRAT diet may make stools firmer and less frequent.
- More severe bowel symptoms are treated with steroids. Infliximab or vedolizumab may be added if needed.
- ICI therapy can cause the liver to become inflamed (hepatitis). This does not often cause symptoms.
- Blood tests are used to monitor liver enzyme levels. If they become too high, steroids are needed.



### **Let us know what you think!**

Please take a moment to complete an online survey about the NCCN Guidelines for Patients.

[NCCN.org/patients/response](https://www.nccn.org/patients/response)

# 5

## Hormones

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- 27 Pituitary
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- 30 Key points





Immune checkpoint inhibitors (ICIs) can affect organs and glands that make hormones. Hormone-related side effects are fairly common. They are also usually permanent. Stopping immunotherapy does not reverse them.

Hormones are substances that travel in blood. They regulate many important body functions. Unlike other side effects of immunotherapy, hormone problems are not treated with steroids.

## Thyroid

The thyroid is a gland in the neck. It makes two main hormones—thyroxine (T4) and triiodothyronine (T3). Together they are often called simply “thyroid hormone.” Among other jobs, thyroid hormone controls metabolism. Metabolism is how fast food becomes fuel for the body. Thyroid hormone levels will be checked with blood tests during immunotherapy.

### Thyroiditis

Painless irritation of the thyroid gland caused by immune attack is called thyroiditis. The most common type is Hashimoto’s thyroiditis. Immune attack first causes hormone levels to rise. This does not often cause symptoms. If it does, you may have:

- Weight loss
- Fatigue
- Fast or abnormal heartbeat
- Sweating
- Anxiety

If you have symptoms, your doctor may prescribe a beta-blocker. This type of drug blocks the effects of stress hormones on the heart.

After 4 to 6 weeks, thyroid hormone levels usually drop. But they drop too low. This is hypothyroidism or underactive thyroid. Symptoms include:

- Weight gain
- Constipation
- Dry skin
- Sensitivity to the cold

You will be prescribed a medicine that replaces thyroid hormone. It is called levothyroxine. It is taken as a pill once a day. Determining the right dose for you can take some trial and error.

## Pituitary

The pituitary is a gland in the brain. It makes hormones that control other glands and body functions. If the pituitary becomes inflamed, it does not make enough of certain hormones. The problems that can result are described below. Permanent damage to the pituitary can occur.

Testing for pituitary problems includes blood tests and sometimes magnetic resonance imaging (MRI) of the brain.

### Secondary adrenal insufficiency

This condition occurs when the pituitary does not make enough adrenocorticotropic hormone (ACTH). As a result, glands on top of the



kidneys (adrenal glands) do not make enough cortisol. Cortisol helps the body respond to stress, fight infection, and regulate blood sugar. The most common symptoms of low cortisol due to pituitary damage include:

- Fatigue
- Loss of appetite
- Muscle weakness

Secondary adrenal insufficiency is managed with medication to replace the hormones not being made by the body. This includes hydrocortisone tablets to replace natural cortisol. They may be needed for the rest of your life. Your doctor will determine the lowest dose needed to prevent symptoms.

Normally, the adrenal glands make much more cortisol at certain times. This happens when there is infection, illness, injury, or trauma to the body. In these cases your dose of hormone replacement therapy may be temporarily increased. Wearing a medical alert bracelet is recommended for this pituitary problem.

Rarely, the level of cortisol can become dangerously low. This is known as an adrenal crisis. In-hospital care is needed. Symptoms of adrenal crisis are listed in [Guide 3](#).

### Central hypothyroidism

This is a rare form of underactive thyroid. In this type the level of thyroid hormone is too low due to a problem with the pituitary or hypothalamus. The symptoms are the same as those normally seen with underactive thyroid. Weight gain, constipation, dry skin, and sensitivity to cold are most common. Your doctor will prescribe levothyroxine. This medication replaces thyroid hormone.

### Guide 3

#### Adrenal crisis symptoms

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Severe fatigue

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Nausea/vomiting

---

Low blood pressure

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Confusion

---

Feeling sleepy or tired

---

Headache\*

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Increased sensitivity to light\*

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Vision changes\*

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*\*Symptom is sometimes present*

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## Pancreas

The pancreas is a gland behind the stomach. One of its jobs is to make a hormone called insulin. Insulin absorbs glucose (sugar) into cells for use as energy. If the pancreas becomes inflamed or damaged, it does not make enough insulin. This is type I diabetes. It is a rare side effect of immunotherapy.

Type I diabetes requires daily insulin therapy for life. Living with diabetes can be hard, but managing it has come a long way. There are new ways to monitor and manage blood sugar. Many people find continuous glucose monitors (CGM) to be an easy way to check blood sugar.

Blood tests are used to monitor for type 1 diabetes. Your blood sugar level will be checked each time you receive immunotherapy. Further testing will be ordered if the blood sugar level is too high. Testing is also needed if you have symptoms of a diabetic emergency, described next.

### Guide 4

#### Diabetic ketoacidosis symptoms

Vomiting

Confusion

Abdominal pain

Increased heart rate

Fruity odor on the breath

Diabetic ketoacidosis (DKA) is a blood sugar crisis. It occurs when blood sugar becomes very high. Fat is broken down too quickly and toxic acids (ketones) build up in the blood and urine. It can be life-threatening if insulin is not received. DKA symptoms are listed in [Guide 4](#).

### The pancreas

**The pancreas is a large gland behind the stomach. During immunotherapy the immune system can attack the pancreas. This causes damage that affects hormone levels.**



## Key points

- The thyroid, pituitary, and/or pancreas may become inflamed during immunotherapy.
- Damage to these glands and organ disrupts hormone levels and causes health problems.
- Hormone problems are usually permanent. Stopping immunotherapy does not reverse them.

### Thyroid

- Thyroiditis is painless injury to the thyroid gland. Thyroid hormone levels may rise for a short time and then often drop.
- Symptoms of too much thyroid hormone can include weight loss, fatigue, and anxiety. Symptoms are not common.
- Symptoms of low thyroid hormone (underactive thyroid) include weight gain, dry skin, and constipation.
- Underactive thyroid is treated with a medicine that replaces thyroid hormone.

### Pituitary

- Low cortisol due to pituitary damage is called secondary adrenal insufficiency.
- Symptoms include fatigue, loss of appetite, and muscle weakness.
- Secondary adrenal insufficiency is treated with hydrocortisone tablets to replace natural cortisol.
- An adrenal crisis can occur if cortisol gets very low. Symptoms include severe fatigue, nausea/vomiting, and headache.

### Pancreas

- Type I diabetes is a rare side effect of immunotherapy. It occurs when the pancreas stops making insulin.
- Lifelong treatment with insulin is needed for type I diabetes. Newer options for monitoring blood sugar are available.
- Diabetic ketoacidosis is a diabetic emergency. It can occur if blood sugar becomes dangerously high.

# 6

## Lungs

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32 Testing

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33 Treatment

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34 Key points





The lungs can become inflamed during immunotherapy. This is called pneumonitis. The most common symptom is trouble breathing. Other symptoms include dry (mucus-free) cough, fever, and chest pain. Pneumonitis can typically be seen on imaging tests, even in those without symptoms.

## Testing

The first sign of pneumonitis is often a low level of oxygen in the blood. In addition to a physical exam, you will have a fast and painless oxygen saturation test. This is done using a small device called a pulse oximeter placed on your fingertip. The oxygen saturation level will be measured when you are at rest (not moving) and also after walking.

Depending on your symptoms (if any) and how severe they are, you may also have some or all of the testing described next.

### Testing for infection

It can be helpful to rule out infection as the cause of pneumonitis, especially in more severe cases. Testing for infection may include:

- Swabbing the inside of your nose to detect viruses, such as the flu and COVID-19
- Phlegm (mucus) culture test
- Blood culture test
- Urine test

Another test that can help rule out infection is bronchoscopy. Bronchoscopy is an imaging technique that allows your doctor to see inside your lungs.

### Pulse oximetry

A pulse oximeter measures the amount of oxygen being carried by red blood cells. It does this by shining light through your finger.



A thin, flexible tube with a tiny light and camera is used. It is guided into your lungs through your nose or mouth. A small amount of sterile saline (saltwater) is put through the tube into the lungs. The saline washes the airway and is then suctioned back through the tube. This is called a bronchoalveolar lavage (BAL). The collected fluid is sent to a lab for testing. If there is a chance that cancer has spread to the lungs, a biopsy may be performed during bronchoscopy.

### Computed tomography (CT)

A CT or “CAT” scan of your chest may be ordered to rule out other causes of your symptoms. If so, a liquid called a contrast agent will also be used. It will either be put directly into your bloodstream through a vein, or given to you to drink. It will help make the CT images clearer.

## Treatment

### No symptoms

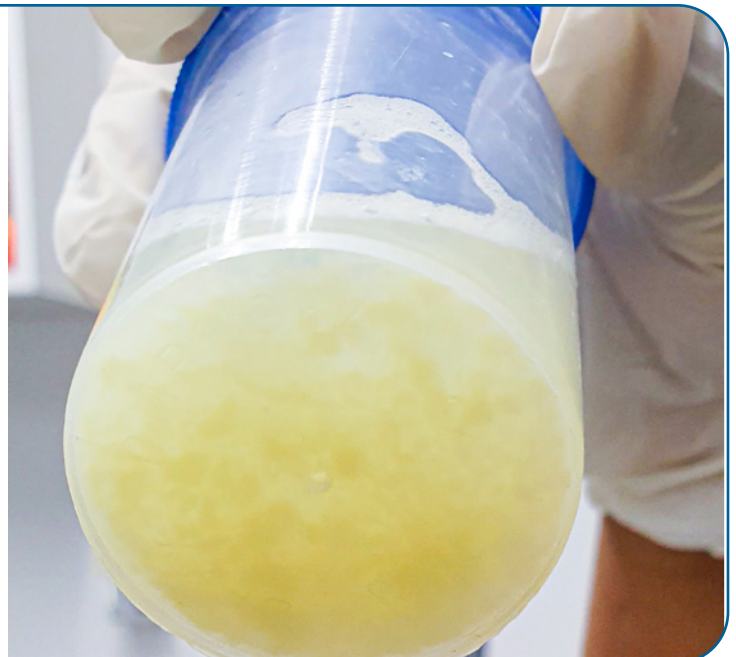
Pneumonitis that does not cause symptoms but can be seen on imaging tests is considered mild. A chest CT may be ordered. You will likely have a follow-up visit in 1 to 2 weeks to see if there is improvement. If you had a CT scan, you may have another 4 to 6 weeks later, or if you start having symptoms. Your doctor may recommend pausing ICI therapy for mild pneumonitis.

### Mild or moderate symptoms

Pneumonitis symptoms include shortness of breath, cough, chest pain, and fever. If you have symptoms, immunotherapy will be paused. You may have noninvasive testing for infection, bronchoscopy with BAL, and/or a chest CT. Treatment with steroids will be started. Your doctor will check your symptoms and oxygen saturation about every 3 to 7 days. If infection has not been ruled out, you may be

### Bronchoalveolar lavage

During a bronchoscopy, a small amount of sterile saline (saltwater) may be put into the lungs. The saline “washes” the airway and is then suctioned back through the tube. The fluid is tested for infection.





prescribed an antibiotic while waiting for test results. If you had a chest CT, you may have another in a few weeks.

### **Severe or life-threatening symptoms**

Pneumonitis is considered severe if you need extra oxygen to breathe and your symptoms are preventing basic self-care. A very serious breathing crisis is considered life-threatening pneumonitis. In-hospital care is needed for both. Immunotherapy will be stopped.

You will have testing for infection. Both minimally invasive methods (eg, nasal swab) and bronchoscopy with BAL are often performed. You may be evaluated by a heart expert (cardiologist). The goal is to rule out heart problems as the cause of your symptoms. If infection has not been ruled out, you may be prescribed an antibiotic while waiting for test results.

IV steroids will be started. If there is no improvement within 48 hours, treatment with one of the following may be added:

- Infliximab
- Intravenous immunoglobulin
- Mycophenolate mofetil

See page 10 for more information on these treatments.

## Key points

- Symptoms of inflamed lungs (pneumonitis) include trouble breathing, dry cough, fever, and chest pain.
- Testing for infection often includes a nasal swab to detect viruses and testing of your mucus, blood, and urine.
- Other testing may include bronchoscopy with bronchoalveolar lavage (BAL) and a chest CT.
- Mild pneumonitis can be seen on imaging tests but does not cause symptoms. ICI therapy can often be continued.
- Steroid therapy is needed for pneumonitis that is causing symptoms. Immunotherapy will be paused until symptoms are gone.
- In-hospital care and treatment with steroids is needed for severe or life-threatening pneumonitis. ICI therapy will be stopped.

# 7

## Muscles and joints

- 36 Inflammatory arthritis
- 37 Muscle pain and weakness
- 38 Polymyalgia rheumatica and giant cell arteritis
- 39 Key points



Immunotherapy can cause joints, tendons, ligaments, bones, and muscles to become inflamed. This chapter describes these side effects and their treatment.

Blood tests can provide helpful information about muscle and joint problems. Blood tests often ordered for these conditions include:

- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Rheumatoid factor (RF)
- Anti-nuclear antibodies (ANA)
- Anti-cyclic citrullinated peptide (anti-CCP)
- Comprehensive metabolic panel (CMP)
- Creatine kinase (CK) and aldolase
- Troponin

The tests that are ordered for you will depend on the suspected problem.

## Inflammatory arthritis

Inflammatory arthritis is not a single disease. It is a group of disorders caused by immune attack on joints. Major types include:

- Rheumatoid arthritis
- Psoriatic arthritis
- Gout
- Lyme disease
- Lupus

Inflammatory arthritis is not the same as osteoarthritis, which is caused by use of the joint(s) over many years. Also, inflammatory arthritis often affects joints throughout the body, rather than one or two joints. Symptoms include:

- Joint pain and swelling
- Tendon pain and swelling
- Stiffness after rest
- Improvement with heat

Your doctor will examine the painful or swollen joints to see how they function. In addition to blood tests, you may have imaging of the affected joints. An x-ray, ultrasound, or magnetic resonance imaging (MRI) may be ordered. Your doctor may also consult with a specialist in arthritis and similar conditions (a rheumatologist).

### Mild symptoms

If only one joint is affected or if pain is mild, nonsteroidal anti-inflammatory drugs (NSAIDs) are used to help relieve symptoms. Ibuprofen, aspirin, and naproxen are NSAIDs. Other medications may also be considered. These include COX2 inhibitors (a newer type of NSAID) and gabapentinoids.

A low-dose oral steroid may be prescribed if there is no improvement. Steroid injections may also be an option for relieving symptoms. This will depend on the number and location of inflamed joints. Steroids are injected directly into the painful or swollen joints with a needle.

### Moderate symptoms

Symptoms that are worse than mild but not severe are called moderate. Treatment with

an oral steroid is recommended. It is typically taken for 2 to 3 weeks. Immunotherapy is sometimes paused for moderate symptoms.

### Severe symptoms

Symptoms are severe if they are stopping you from doing everyday tasks. Imaging tests also show joint erosion in severe arthritis. Severe arthritis can lead to permanent joint damage.

Steroids will be started. If there is no improvement in about a week, treatment with other drugs may be added. The type of drugs used are called DMARDs. This is short for disease-modifying anti-rheumatic drugs. Immunotherapy will be paused.

## Muscle pain and weakness

ICI therapy can cause muscle pain and weakness. Muscle pain is called myalgia. Muscle weakness is called myositis.

Blood tests and muscle strength testing will be ordered. Muscle strength testing helps detect nervous system problems that may be causing muscle weakness.

### Treatment

NSAIDs and other non-opioid medications can help relieve mild muscle pain. Immunotherapy is sometimes paused for mild symptoms. You will have blood tests on a regular basis to check the levels of creatine kinase and aldolase.

Immunotherapy will be paused for moderate, severe, or life-threatening symptoms. Your doctor may order electromyography (EMG) or

MRI of the affected muscle(s). EMG measures muscle and nerve function.

Steroid therapy will be started and continued until symptoms are gone. Creatine kinase and aldolase levels will be monitored during steroid therapy. Treatment with intravenous immunoglobulin (IVIG) may be added if needed.

Managing severe muscle pain is important. Your doctor will make recommendations for treating or managing your pain.

For symptoms that do not improve with steroids, more testing and treatment are needed. A tiny piece of muscle may be removed for testing. Treatment with plasmapheresis or one of the following may be added:

- Infliximab
- Rituximab
- Mycophenolate mofetil

See page 10 for more information on these treatments.

## Polymyalgia rheumatica and giant cell arteritis

Polymyalgia rheumatica (PMR) is a disorder that causes muscle aches, pain, or stiffness. The shoulders are most often affected. Signs and symptoms often come on quickly and are worse in the morning.

PMR is closely related to another condition called giant cell arteritis (GCA). Many people who have one of these conditions also have symptoms of the other. In GCA, blood vessels become inflamed and more narrow. The arteries on the sides of the forehead (the temples) are most often affected. These are called the temporal arteries. If left untreated, GCA can lead to stroke or blindness.

Symptoms of GCA include:

- Changes in eyesight
- Headache
- Scalp tenderness
- Jaw pain from chewing or prolonged speaking

Blood and lab tests are used to gather more information about possible PMR or GCA. If your doctor suspects PMR based on your symptoms, you may have an ultrasound of your shoulders, hips, or both.

If you have symptoms of GCA, such as headaches or vision problems, you may have an ultrasound and a biopsy of your temporal artery. In a temporal artery ultrasound, sound probes are placed on the sides of the head and under each arm. A temporal artery biopsy is a minor procedure performed under local

### Polymyalgia rheumatica

**PMR causes muscle aches, pain, or stiffness, especially in the shoulders. In addition to blood tests, you may have an ultrasound of your shoulders, hips, or both to look for signs of PMR.**



anesthesia. A tiny piece of scalp artery is removed for testing.

### **PMR treatment**

Six weeks of oral steroid therapy is recommended for mild pain and/or stiffness. If symptoms are limiting your ability to do everyday tasks, immunotherapy will be paused. A higher dose of oral steroids will be started. When symptoms are gone, steroids will be tapered over 6 to 12 weeks (maybe longer). If there is no improvement with steroids, you may be referred to a specialist.

### **GCA treatment**

Immunotherapy will be paused for GCA. Steroids will be started and continued until symptoms are gone. While steroid therapy should always be stopped slowly, it is stopped extra slowly for GCA. The tapering period is at least 8 to 12 weeks.

If you are having eye or vision symptoms, you may have pulse therapy. This is the use of high doses of IV steroids given over a short period, usually a few days. Pulse therapy can boost the helpful effects of steroids while reducing the harmful effects.

In some cases, treatment with methotrexate or tocilizumab may be added. Your doctor may consult with both an ophthalmologist and a rheumatologist in order to guide treatment for GCA.

## **Key points**

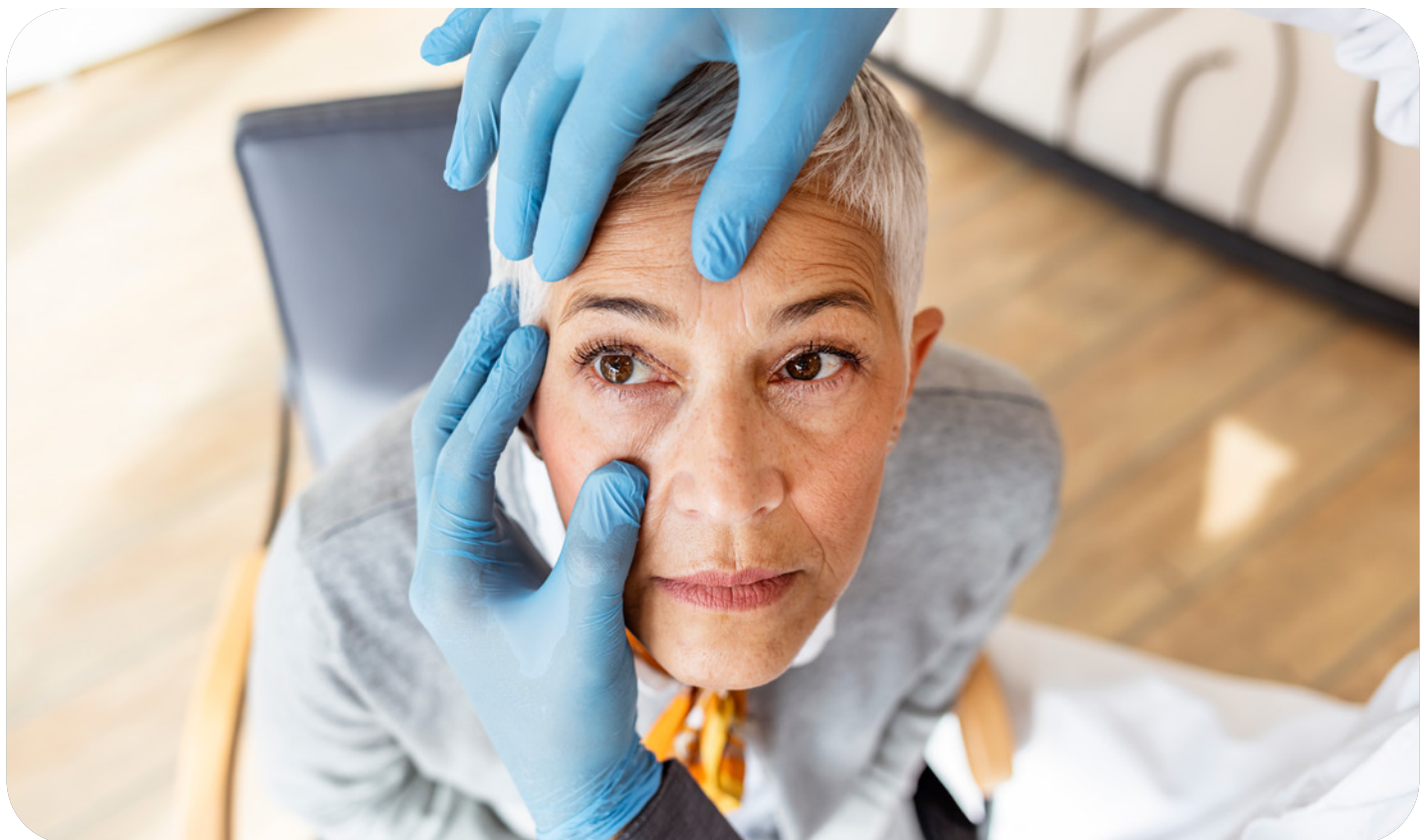
- Inflammatory arthritis is a group of joint disorders that includes rheumatoid and psoriatic arthritis.
- Immunotherapy can usually be continued for mild inflammatory arthritis. NSAIDs can help with symptoms.
- Steroid injections may be an option for relieving arthritis symptoms.
- Severe muscle pain and/or weakness requires treatment with steroid therapy.
- PMR causes muscle aches, pain, or stiffness, especially in the shoulders.
- GCA is a related problem in which blood vessels in the temples are inflamed.
- GCA symptoms include changes in eyesight, headache, scalp tenderness, and jaw pain.
- Immunotherapy will be stopped for GCA. Steroid therapy is needed.



# 8

## Less common side effects

- 41 Nervous system
- 43 Heart and blood vessels
- 44 Eyes
- 45 Kidneys
- 46 Pancreas
- 47 Key points



Immunotherapy can have less common but serious effects on the nervous system, heart, kidneys, eyes, and pancreas. This chapter describes these uncommon but possibly severe problems.

## Nervous system

Nervous system side effects of ICI therapy are rare but serious. They can affect the brain, spinal cord, and nerves throughout the body.

Testing is needed to diagnose nervous system problems. Blood tests will be ordered. Most people will also have several of the following:

- Magnetic resonance imaging (MRI) of the brain and/or spine
- Electromyography (EMG) and nerve conduction studies (NCS)
- Lung function and breathing tests
- Heart function tests, such as an electrocardiogram (ECG)
- Lumbar puncture
- Electroencephalogram (EEG)

A main goal of testing is to rule out bacteria and viruses as the cause of your symptoms.

### Myasthenia gravis

Myasthenia gravis is a disease that causes muscle weakness. It can weaken face, throat, and eye muscles. Symptoms include:

- Droopy eyelids
- Double vision
- Problems swallowing
- Weak face muscles
- Weak breathing muscles
- Weakness in the arms and legs

In-hospital treatment is needed for moderate or severe myasthenia gravis. For moderate symptoms a drug called pyridostigmine is given. It is a muscle strengthener. It works by raising the levels of a chemical in the nervous system. Oral steroids may also be given.

Severe myasthenia gravis is treated with steroids. Either plasmapheresis or intravenous immunoglobulin (IVIG) is also given. If needed, treatment with rituximab may be added. See page 10 for more information on these treatments.

### Guillain-Barré syndrome (GBS)

GBS is a nerve problem. It can cause weakness of the arms, legs, face, breathing muscles, and eye nerves. The first symptom is often pain in the lower back and thighs. In-hospital treatment is needed.

When caused by immunotherapy, GBS is treated with IV steroids and either IVIG or plasmapheresis. You will be monitored closely in the hospital. There are options for managing pain. Gabapentin, pregabalin, or duloxetine may be given.

### Non-infectious meningitis

The meninges are the thin layers of tissue that cover the brain and spinal cord. When they become inflamed, it is called meningitis. When not caused by infection, it is known as aseptic or non-infectious meningitis.

Symptoms can include:

- Headache
- Sensitivity to light
- Neck stiffness
- Fever
- Nausea or vomiting

ICI therapy will be paused if you have symptoms of meningitis. Symptoms are considered severe if they are making self-care difficult. In-hospital care is needed. If infection has been ruled out, steroids may be started. Or, you may be closely monitored without steroids.

### Inflamed brain

ICI therapy can cause the brain to become inflamed. This rare side effect is called encephalitis. Symptoms range from mild confusion to serious brain function problems.

[See Guide 5.](#)

Immunotherapy will be paused if you have symptoms. Symptoms are considered severe if they are making self-care difficult. In-hospital care is needed for encephalitis that is severe or worse. Treatment with IV steroids will be started.

If steroids are not enough, either IVIG or plasmapheresis is given. Sometimes treatment with rituximab is added. This may be the case

if your blood has a specific protein or if there is no improvement.

### Inflamed spinal cord

The spinal cord carries messages between the brain and nerves in the body. If it becomes inflamed, these messages are blocked.

This is called transverse myelitis. It causes problems with sensation and nerve function. Symptoms include pain, muscle weakness in the legs (sometimes the arms), and sensory problems. Bladder and bowel problems are also common.

In-hospital care is needed. Treatment with IV steroids will be started. Either IVIG or plasmapheresis is often also given.

## Guide 5 Encephalitis symptoms

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Confusion

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Changes in behavior

---

Headaches

---

Seizures

---

Short-term memory loss

---

Problems reacting or responding

---

Trouble speaking

---

## Heart and blood vessels

Heart and blood vessel side effects of immunotherapy are rare, but can come on quickly and become very severe.

Immunotherapy can cause the heart muscle to become inflamed. This is called myocarditis. This is a rare but potentially severe side effect of ICI treatment. The heart becomes bigger (swollen) and weaker. Severe cases can lead to heart failure and changes in heartbeat. In people not on immunotherapy, it is usually caused by infection.

The outer lining of the heart (pericardium) can also become inflamed. This is called pericarditis. Fluid can build up around the heart (pericardial effusion) and may need to be removed. Arteries and veins are blood vessels. Inflammation of blood vessels is also possible. This is called vasculitis.

Immunotherapy can also cause plaque to worsen in cancer survivors. Plaque is a buildup of fats, cholesterol, and other substances in heart arteries. Steps to prevent and treat high cholesterol, diabetes, and high blood pressure are important for people on ICI therapy.

Symptoms of myocarditis include:

- Fatigue
- Chest pain or pressure
- Very slow, very fast, or irregular heartbeat
- Shortness of breath
- Swollen legs, ankles, or feet
- Lightheadedness

If you have symptoms you will need to be examined by a heart expert (cardiologist or cardio-oncologist). Your blood pressure, heart rate, and blood oxygen level will be measured. Additional testing to look for heart and blood vessel problems is needed. Testing may include some or all of the following:

- Blood tests
- Electrocardiogram (ECG)
- Echocardiogram
- Cardiac MRI
- Cardiac catheterization
- Removal of a sample of heart tissue for testing (endomyocardial biopsy)

The goal is to find heart problems early and learn if they are due to immunotherapy or other heart or blood vessel diseases. You may need to be admitted to the hospital for closer monitoring, to do more advanced tests, or for treatment.

Myocarditis is treated with high-dose IV steroids. You will be closely monitored. If there is no improvement in 1 to 2 days, other immune-suppressing treatments may be added. These may include:

- Intravenous immunoglobulin (IVIG)
- Infliximab
- Abatacept
- Mycophenolate mofetil
- Plasmapheresis

See page 10 for more information on these treatments. Heart (cardiac) medications may be required. You will be switched from

IV to oral steroids. Steroids will then be slowly stopped (tapered). Other drugs will then be given to replace steroids. During steroid tapering you will be monitored using blood tests, electrocardiogram (ECG), echocardiogram, and cardiac MRI. The goal is to reverse immune attack against the heart muscle, support and recover heart function, and prevent the myocarditis from recurring.

Damage to the heart muscle can lead to changes in heartbeat. Electrical defibrillation treatment and/or a pacemaker may be needed. This small device is implanted in the chest. It helps the heart to function. It may be needed permanently.

## Eyes

A number of symptoms can signal an eye-related problem. The most common are uveitis (described below) and dry eyes. [See Guide 6.](#)

Over-the-counter eye drops (“artificial tears”) can help with dryness and irritation. These saline (salt)-based drops feel like real tears. They moisturize and soothe the eyes. Contact lenses and eye makeup can make symptoms worse. Try to avoid these and other irritants.

Steroid eye drops are often all that is needed for mild symptoms. More severe symptoms may require steroids and pausing ICI therapy. If you have symptoms or vision changes, you will have a complete eye exam by an ophthalmologist. This eye expert will guide your care. Blood tests to look for infection and other causes are recommended.

### Guide 6 Eye and vision symptoms

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Blurred/distorted vision

---

Blind spots

---

Change in color vision

---

Sensitivity to light

---

Tenderness or pain

---

Eyelid swelling

---

Bulging eyes

---

Red or purple discoloration of the eye

---

New floaters

---

Itchy eyes

---

Eye redness

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### Episcleritis

The thin, outer layer of the eye is the episclera. If this layer becomes inflamed it does not usually affect eyesight. Treatment is not always needed. Artificial tears can help with symptoms. If the inflammation is mild, immunotherapy is typically continued.

If there are changes in eyesight, immunotherapy will be paused. Treatment may include NSAID eye drops, steroid eye drops, or an oral steroid.

### Scleritis

The sclera is the white of the eye. It protects the eye and helps maintain its structure. When the sclera is inflamed it is often painful. Other



symptoms include eye tenderness, redness, and swelling.

Scleritis is considered mild if it does not affect vision. Mild scleritis is treated with an oral NSAID. Oral steroids are needed for scleritis that is causing vision changes. Immunotherapy will be paused.

### **Uveitis**

The layer of tissue beneath the white of the eye is called the uvea. It has 3 parts. When any of these parts is inflamed, it is called uveitis. If not treated, serious problems such as blindness can occur.

The part of the uvea that most often becomes inflamed is the iris. This is the colored ring around the pupil. ICI therapy will be paused for iritis. Treatment with steroid drops is recommended. An oral steroid may also be

prescribed. The iris is the front part of the uvea. For this reason, iritis is also called anterior (“near the front”) uveitis.

Inflammation of the back of the uvea or of all three parts is less common. It is also more serious. Immunotherapy will be paused. Treatment with steroid eye drops, steroid eye injections, or oral steroids is recommended.

### **Kidneys**

The kidneys filter blood. They remove waste and extra water. One substance filtered out is creatinine. Creatinine is a waste product of muscles. A high level can be a sign that the kidneys are not working well. No treatment is needed for small rises in creatinine. The level

### **Slit lamp eye exam**

Examination with a microscope with a bright light (a “slit lamp”) is an essential part of a full eye and vision exam.





of creatinine in blood and protein in your urine (pee) will be monitored.

If creatinine goes up a lot, causes other than immunotherapy will be considered. If they are ruled out, oral steroids will be started. Immunotherapy will be paused. Creatinine and urine protein levels will be monitored. A small piece of tissue may be removed from your kidney for testing before starting steroids. This is called a kidney biopsy.

Urine protein and creatinine levels should normalize within 4 to 6 weeks of steroid therapy. If not, other immune-suppressing treatments may be added.

If you develop signs of acute kidney damage, your doctor will review your medications. This includes prescription and over-the-counter drugs. Some drugs can damage the kidneys if taken at high doses for a long time. Use of such drugs will be avoided or limited. Others will be adjusted based on how well your kidneys are working.

### Acute kidney injury

This problem occurs when the kidneys suddenly stop filtering blood. Wastes build up and disrupt blood's chemical makeup. This kidney crisis comes on quickly, usually in less than a few days. Symptoms include:

- Making less urine
- Swollen legs, ankles, or feet
- Shortness of breath
- Fatigue
- Confusion
- Nausea

- Chest pain or pressure
- Seizures or coma in severe cases

In-hospital care is usually needed. Treatment with steroids will be started. You may first have a kidney biopsy. Immunotherapy will be paused.

## Pancreas

On top of making hormones, the pancreas also makes substances that help digest food. These are called enzymes. When inflamed or injured, liver cells leak more enzymes than normal into the bloodstream.

Blood tests are used to monitor enzyme levels during immunotherapy. Treatment is not needed for small increases. Any symptoms are usually mild and may include:

- Nausea
- Bloating
- Burping
- Pain in abdomen
- Back pain

High levels of these substances can be a sign of acute pancreatitis. In autoimmune pancreatitis the pancreas becomes very inflamed over a short period of time. This is rare during immunotherapy.

Imaging with CT and sometimes a special type of MRI is ordered if this problem is suspected. In-hospital care is needed for acute pancreatitis. Treatment involves steroids and IV fluids.

## Key points

- Problems affecting the nervous system, heart, eyes, kidneys, and exocrine pancreas are rare but serious.

### Nervous system

- Myasthenia gravis causes muscle weakness. Symptoms include droopy eyelids, double vision, and trouble swallowing.
- Guillain-Barré syndrome is a nerve problem that can weaken the arms, legs, face, breathing muscles, and eye nerves.
- Symptoms that the brain is inflamed (encephalitis) include confusion, changes in behavior, headaches, and seizures.
- Aseptic meningitis can cause headache, sensitivity to light, neck stiffness, fever, and nausea/vomiting.

### Heart and blood vessels

- Myocarditis is a rare but severe and progressive condition in which the heart muscle becomes inflamed. It can lead to heart failure and abnormal heart rhythms causing the heart to stop.
- Pericarditis is a condition in which the lining around the heart becomes inflamed. It causes fluid to build up around the heart (pericardial effusion).
- Symptoms of a heart problem include worsening fatigue, chest pressure or pain, shortness of breath, heartbeat changes, and swelling of the legs, ankles, or feet.
- Immunotherapy can increase plaque buildup in cancer survivors. Preventive

cardiovascular care is needed in addition to cancer treatment.

### Eyes

- If you have symptoms or vision changes, you will have a full eye exam by an ophthalmologist.
- The most common side effects are dry eye and inflammation of the inside of the eye (uveitis).
- Eye pain can be a sign that the white of the eye is inflamed (scleritis). Other symptoms include tenderness, redness, and swelling.

### Kidneys

- Acute kidney injury is a serious and fast-developing problem. It occurs when the kidneys suddenly stop filtering blood.
- Symptoms include making less urine, lower body swelling, shortness of breath, fatigue, confusion, and nausea.

### Pancreas

- The levels of substances made by the pancreas will be checked using blood tests.
- High levels can be a sign of acute pancreatitis. This is rare and requires in-hospital care.

# 9

## Resources

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49 Questions to ask

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51 Websites



Immune checkpoint inhibitors (ICIs) are the most widely used type of cancer immunotherapy. This chapter includes resources for learning more about ICIs and their effects.

ICIs now play a major role in cancer care. They are used to treat many different types of cancer. While their anti-cancer benefits are important, they come with unique side effects.

Knowing the possible side effects of ICI therapy can help you to notice symptoms early and report them to your care team.

## Questions to ask

It is normal to have lots of questions about immunotherapy. Possible questions to ask your treatment team are listed on the following pages. Feel free to use these questions or come up with your own.

A list of resources follows the questions. These websites provide information for patients about ICIs and their effects.



## When to contact your cancer care team

- ✓ If you develop signs and symptoms, such as:
  - Severe fatigue
  - Headache
  - Rash
  - Cough
  - Shortness of breath
  - Chest pain
  - Abdominal bloating
  - Change in bowel habits
  - Weight loss
  - Vision changes or eye pain
  - Severe muscle weakness
  - Severe muscle or joint pains
  - Mood changes
- ✓ If you are seen by a new health care provider
- ✓ If you are prescribed any new medication
- ✓ If you are admitted to the hospital
- ✓ Before getting any immunizations or vaccinations





## Websites

### AIM with Immunotherapy

[aimwithimmunotherapy.org](http://aimwithimmunotherapy.org)

### Be the Match

[BeTheMatch.org](http://BeTheMatch.org)

### CancerCare

[cancercares.org](http://cancercares.org)

### Cancer Research Institute

[cancerresearch.org/en-us/patients](http://cancerresearch.org/en-us/patients)

### Cancer Support Community

[cancersupportcommunity.org](http://cancersupportcommunity.org)

### Good Days

[mygooddays.org](http://mygooddays.org)

### National Coalition for Cancer Survivorship

[canceradvocacy.org](http://canceradvocacy.org)

### Oncology Nursing Society

Immunotherapy Wallet Cards

[ons.org/clinical-practice-resources/immunotherapy-patient-wallet-card](http://ons.org/clinical-practice-resources/immunotherapy-patient-wallet-card)

### PAN Foundation

[panfoundation.org](http://panfoundation.org)

### Society for Immunotherapy of Cancer (SITC)

[sitcancer.org/connectedold/p/patient](http://sitcancer.org/connectedold/p/patient)

### Stupid Cancer

[stupidcancer.org](http://stupidcancer.org)

### The Leukemia & Lymphoma Society

[lls.org](http://lls.org)

### The Myositis Association

[myositis.org](http://myositis.org)

### NCCN

Understanding Immunotherapy Side Effects Infographic

[NCCN.org/images/pdf/Immunotherapy\\_Infographic.pdf](http://NCCN.org/images/pdf/Immunotherapy_Infographic.pdf)

### U.S. National Library of Medicine Clinical Trials Database

[clinicaltrials.gov](http://clinicaltrials.gov)

Immunotherapy side effects can happen even after treatment is over. Stay alert for new symptoms for at least 1 year after finishing immunotherapy.



## Words to know

**aseptic meningitis**

Inflammation of the tissues covering the brain and spinal cord that is not caused by a bacterial infection.

**blister**

A fluid-filled sac in the outer layer of skin.

**colitis**

Inflamed bowel (colon). A common side effect of ICIs.

**CTLA-4**

A protein found on T cells that helps keep the body's immune responses in check. The immune checkpoint inhibitor ipilimumab is used to block CTLA-4.

**diabetic ketoacidosis (DKA)**

A diabetic emergency. Occurs when blood sugar drops dangerously low. Toxic acids (ketones) collect in the blood and urine.

**diarrhea**

Frequent and watery bowel movements. A common side effect of ICI therapy.

**encephalitis**

Inflammation of the brain. A rare side effect of ICI therapy.

**episcleritis**

Inflammation of the thin outer layer of the eye. A rare side ICI effect.

**giant cell arteritis (GCA)**

Inflammation of the lining of the arteries, especially the arteries in the temples.

**Guillain-Barré syndrome (GBS)**

A rare condition in which the body's immune system attacks the nerves located outside the brain and spinal cord.

**hepatitis**

Inflamed liver. Does not often cause symptoms.

**hypothyroidism**

A condition in which the thyroid gland does not make enough thyroid hormone. Also called underactive thyroid.

**immune checkpoint inhibitor (ICI)**

A type of cancer treatment that blocks contact between immune cells and cancer cells. The most common type of immunotherapy.

**immune-related adverse event (irAE)**

A side effect of cancer immunotherapy.

**inflammatory arthritis**

A group of disorders caused by immune attack on joints. Includes rheumatoid and psoriatic arthritis.

**intravenous immunoglobulin (IVIG)**

IV infusion of helpful antibodies collected from many donors.

**maculopapular rash**

A rash with both flat patches and bumps. A common side effect of ICIs.

**myalgias**

Pain in a muscle or group of muscles.

**myasthenia gravis**

A disease that causes weakness in the arms and legs, vision problems, and drooping eyelids or head.

**myocarditis**

A condition in which the heart muscle becomes inflamed. The heart may also become enlarged, weak, and abnormal heartbeat may occur. A very rare but severe ICI side effect.

**myositis**

Weakness, swelling, and/or pain due to inflamed muscles.

**nonsteroidal anti-inflammatory drug (NSAID)**

A drug that decreases fever, swelling, pain, and redness. Also called NSAID.

**pancreatitis (acute)**

Inflamed pancreas. A rare side effect of ICI therapy.

**PD-1**

A protein found on T cells that helps keep the body's immune responses in check. Some ICIs are used to block PD-1.

**pericardial effusion**

The build-up of fluid around the heart.

**pericarditis**

A condition in which the outer lining of the heart becomes inflamed. Can cause pericardial effusion.

**pneumonitis**

Inflammation of one or both lungs. The most common symptom is trouble breathing.

**polymyalgia rheumatica (PMR)**

A disorder that causes muscle pain and stiffness, especially in the shoulders.

**pruritus**

Itchy skin, with or without a rash. A common side effect of ICI therapy.

**steroids**

Lab-made drugs that slow the immune system. A common treatment for ICI side effects. Short for corticosteroid.

**Stevens-Johnson syndrome (SJS)**

A rare but very serious disorder of the skin and mucous membranes.

**thyroiditis**

Painless injury to the thyroid gland caused by immune attack. Causes thyroid hormone levels to rise temporarily before dropping too low.



**We want your feedback!**

Our goal is to provide helpful and easy-to-understand information on cancer.

Take our survey to let us know what we got right and what we could do better:

[NCCN.org/patients/feedback](https://www.nccn.org/patients/feedback)

**transverse myelitis**

A nervous system disorder in which both sides of one section of the spinal cord are inflamed.

**uveitis**

Inflammation of all or part of the middle layer of the wall of the eye (uvea). A rare ICI side effect.

**vasculitis**

Inflammation of blood vessels (arteries and veins).





# NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Immunotherapy-Related Toxicities, Version 1.2022. It was adapted, reviewed, and published with help from the following people:

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# NCCN Cancer Centers

Abramson Cancer Center  
at the University of Pennsylvania  
Philadelphia, Pennsylvania  
800.789.7366 • [penncancer.org](http://penncancer.org)

Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer  
Center and Cleveland Clinic Taussig  
Cancer Institute  
Cleveland, Ohio  
800.641.2422 • UH Seidman Cancer Center  
[uhhospitals.org/services/cancer-services](http://uhhospitals.org/services/cancer-services)  
866.223.8100 • CC Taussig Cancer Institute  
[my.clevelandclinic.org/departments/cancer](http://my.clevelandclinic.org/departments/cancer)  
216.844.8797 • Case CCC  
[case.edu/cancer](http://case.edu/cancer)

City of Hope National Medical Center  
Los Angeles, California  
800.826.4673 • [cityofhope.org](http://cityofhope.org)

Dana-Farber/Brigham and Women's  
Cancer Center | Massachusetts General  
Hospital Cancer Center  
Boston, Massachusetts  
617.732.5500 • [youhaveus.org](http://youhaveus.org)  
617.726.5130  
[massgeneral.org/cancer-center](http://massgeneral.org/cancer-center)

Duke Cancer Institute  
Durham, North Carolina  
888.275.3853 • [dukecancerinstitute.org](http://dukecancerinstitute.org)

Fox Chase Cancer Center  
Philadelphia, Pennsylvania  
888.369.2427 • [foxchase.org](http://foxchase.org)

Fred & Pamela Buffett Cancer Center  
Omaha, Nebraska  
402.559.5600 • [unmc.edu/cancercenter](http://unmc.edu/cancercenter)

Fred Hutchinson Cancer  
Research Center/Seattle  
Cancer Care Alliance  
Seattle, Washington  
206.606.7222 • [seattlecca.org](http://seattlecca.org)  
206.667.5000 • [fredhutch.org](http://fredhutch.org)

Huntsman Cancer Institute  
at the University of Utah  
Salt Lake City, Utah  
800.824.2073 • [huntsmancancer.org](http://huntsmancancer.org)

Indiana University  
Melvin and Bren Simon  
Comprehensive Cancer Center  
Indianapolis, Indiana  
888.600.4822 • [www.cancer.iu.edu](http://www.cancer.iu.edu)

Mayo Clinic Cancer Center  
Phoenix/Scottsdale, Arizona  
Jacksonville, Florida  
Rochester, Minnesota  
480.301.8000 • Arizona  
904.953.0853 • Florida  
507.538.3270 • Minnesota  
[mayoclinic.org/cancercenter](http://mayoclinic.org/cancercenter)

Memorial Sloan Kettering  
Cancer Center  
New York, New York  
800.525.2225 • [mskcc.org](http://mskcc.org)

Moffitt Cancer Center  
Tampa, Florida  
888.663.3488 • [moffitt.org](http://moffitt.org)

O'Neal Comprehensive  
Cancer Center at UAB  
Birmingham, Alabama  
800.822.0933 • [uab.edu/onealcancercenter](http://uab.edu/onealcancercenter)

Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University  
Chicago, Illinois  
866.587.4322 • [cancer.northwestern.edu](http://cancer.northwestern.edu)

Roswell Park Comprehensive  
Cancer Center  
Buffalo, New York  
877.275.7724 • [roswellpark.org](http://roswellpark.org)

Siteman Cancer Center at Barnes-  
Jewish Hospital and Washington  
University School of Medicine  
St. Louis, Missouri  
800.600.3606 • [siteman.wustl.edu](http://siteman.wustl.edu)

St. Jude Children's  
Research Hospital/  
The University of Tennessee  
Health Science Center  
Memphis, Tennessee  
866.278.5833 • [stjude.org](http://stjude.org)  
901.448.5500 • [uthsc.edu](http://uthsc.edu)

Stanford Cancer Institute  
Stanford, California  
877.668.7535 • [cancer.stanford.edu](http://cancer.stanford.edu)

The Ohio State University  
Comprehensive Cancer Center -  
James Cancer Hospital and  
Solove Research Institute  
Columbus, Ohio  
800.293.5066 • [cancer.osu.edu](http://cancer.osu.edu)

The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins  
Baltimore, Maryland  
410.955.8964  
[www.hopkinskimmelcancercenter.org](http://www.hopkinskimmelcancercenter.org)

The University of Texas  
MD Anderson Cancer Center  
Houston, Texas  
844.269.5922 • [mdanderson.org](http://mdanderson.org)

UC Davis  
Comprehensive Cancer Center  
Sacramento, California  
916.734.5959 • 800.770.9261  
[health.ucdavis.edu/cancer](http://health.ucdavis.edu/cancer)

UC San Diego Moores Cancer Center  
La Jolla, California  
858.822.6100 • [cancer.ucsd.edu](http://cancer.ucsd.edu)

UCLA Jonsson  
Comprehensive Cancer Center  
Los Angeles, California  
310.825.5268 • [cancer.ucla.edu](http://cancer.ucla.edu)

UCSF Helen Diller Family  
Comprehensive Cancer Center  
San Francisco, California  
800.689.8273 • [cancer.ucsf.edu](http://cancer.ucsf.edu)

University of Colorado Cancer Center  
Aurora, Colorado  
720.848.0300 • [coloradocancercenter.org](http://coloradocancercenter.org)

University of Michigan  
Rogel Cancer Center  
Ann Arbor, Michigan  
800.865.1125 • [rogelcancercenter.org](http://rogelcancercenter.org)

University of Wisconsin  
Carbone Cancer Center  
Madison, Wisconsin  
608.265.1700 • [uwhealth.org/cancer](http://uwhealth.org/cancer)

UT Southwestern Simmons  
Comprehensive Cancer Center  
Dallas, Texas  
214.648.3111 • [utsouthwestern.edu/simmons](http://utsouthwestern.edu/simmons)

Vanderbilt-Ingram Cancer Center  
Nashville, Tennessee  
877.936.8422 • [vicc.org](http://vicc.org)

Yale Cancer Center/  
Smilow Cancer Hospital  
New Haven, Connecticut  
855.4.SMILOW • [yalecancercenter.org](http://yalecancercenter.org)

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# Immunotherapy Side Effects

## Immune Checkpoint Inhibitors

### 2022

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