National Comprehensive Cancer Network®

2026

NCCN Guidelines for Patients®

Cancer care recommendations from leading experts at the National Comprehensive Cancer Network® (NCCN®)

Immunotherapy Side Effects:

CAR T-Cell and Lymphocyte Engager Therapies



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NCCN Guidelines for Patients®

The essential guide for people facing cancer.

Based on care recommendations from leading cancer experts.

Explains high-quality cancer care provided at state-of-the-art cancer centers.

Reviewed and revised every year.

Did you know that top cancer centers across the United States work together to improve cancer care? This alliance of leading cancer centers is called the National Comprehensive Cancer Network® (NCCN®).

Because cancer care is always evolving, NCCN develops and frequently updates evidence-based cancer care recommendations used by health care providers worldwide. These recommendations are known as the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).

The NCCN Guidelines for Patients plainly explain these expert recommendations, so you can talk with your care team about the best care for you.

These NCCN Guidelines for Patients are based on the NCCN Guidelines® for Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities, Version 2.2026 — November 11, 2025.

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About CAR T-cell and lymphocyte engager therapies

5 What is CAR T-cell therapy?

5 What is lymphocyte engager therapy?

6 What are some side effects of these therapies?

6 How are side effects treated?

7 How can I get the best care?

Compared to other cancer treatments, chimeric antigen receptor (CAR) T-cell therapy and lymphocyte engager therapy are newer types of treatment used for some cancers.

CAR T-cell and lymphocyte engager therapies are immunotherapies because they use the immune system—your body's defense against disease—to kill cancer cells. But these 2 therapies work in different ways.

As with many cancer treatments, people undergoing immunotherapy may have side effects.

"Every normal activity I do is a sign of what I'm taking back from cancer. The more I am doing normal things, the less I'm the cancer guy, the CAR T guy, and the more I'm just me."



CAR stands for chimeric antigen receptor.

To learn what CAR is, read *Chapter 2: Side effects of CAR T-cell therapy*.

In these guidelines, you'll learn about these treatments, their common possible side effects, and how these side effects are managed and treated. If you have questions about what type of treatment you're starting or getting, talk to your cancer care team. They can tell you about specific side effects you may be at high risk for, and what symptoms you may have.

What is CAR T-cell therapy?

Chimeric antigen receptor (CAR) T-cell therapy is a type of immunotherapy. This therapy works by changing your immune cells in a way that allows them to find and kill cancer cells.

CAR T-cell therapy treats certain blood cancers that did not respond to other treatments or that have come back after treatment. This includes some forms of lymphoma, leukemia, and multiple myeloma.

What is lymphocyte engager therapy?

Lymphocyte engager therapy is another type of immunotherapy. It works by connecting immune cells with cancer cells. When it connects—or engages—the immune cells and cancer cells,

it makes it easier for the immune system to find and kill cancer. Learn more about lymphocyte engager therapy in Chapter 4.

Lymphocyte engager therapy treats certain cancers that didn't respond to other treatments or that have come back after treatment.

What are some side effects of these therapies?

CAR T-cell and lymphocyte engager therapies can affect many body systems and organs, including the:

- Brain and nervous system
- Liver
- Heart
- Digestive system
- Muscles and joints
- Blood and bone marrow
- Kidneys

They can also increase the risk for infection and inflammation. Some side effects cause diarrhea, rash, and headaches. Others can only be found using blood and urine tests and imaging.

Common side effects

The 2 most common side effects of CAR T-cell therapy and lymphocyte engager therapy are:

- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)



Immunotherapy Wallet Card

Ask your cancer care team for an immunotherapy wallet card. This card states that you have received CAR T-cell or lymphocyte engager therapy. It also lists potential side effects and contact numbers for your care team. Always carry it with you. If a card is not available, ask for a printable list of your treatment regimen.

You can read about CRS and ICANS in Chapters 5 and 6.

Other side effects are discussed in Chapters 3 and 4.

How are side effects treated?

These kinds of cancer treatments vary and can affect different body systems and organs. As a result, side effects also vary widely.

Some mild side effects can be treated with acetaminophen (Tylenol) for managing fevers or intravenous (IV) fluids to help with hydration. Intravenous means given by a needle into a vein.

Other treatments can include:

- **Steroids**, which are medicines that reduce immune system activity. They relieve inflammation in the body. Dexamethasone and methylprednisolone are common steroids.
- **Antibiotics** to treat—and in some cases prevent—infections.
- **Immunoglobulin replacement therapy**, which may be given intravenously (called IVIg) or subcutaneously (under the skin). IVIg can help manage overactive or abnormal immune responses that sometimes happen after CAR T-cell therapy. Ig is a protein made by B cells that helps fight infection.
- **Immunosuppressants**, which can also help reduce immune system activity and relieve inflammation.

Other treatments will be discussed in later chapters.

How can I get the best care?

Advocate for yourself. You have an important role to play in your care. Many people feel more satisfied when they actively take part in planning their cancer care.

The NCCN Guidelines for Patients will help you play a larger role in your care. Discuss the recommendations in this guide with your care team. Ask questions about your options and share your goals and concerns.

How this guide can help you

Making decisions about cancer care is stressful. There's a lot to learn, and you don't know what the future holds.

Use this guide to get the information and support you need.

Patients, doctors, and other health care professionals trust the NCCN Guidelines for Patients. This guide uses clear, everyday language to explain current cancer care recommendations made by respected experts in the field. Their recommendations are based on the latest research and practices at leading cancer centers.

Your health is unique to you, so your cancer care should be, too. As you read this guide, you'll learn which treatments are likely to provide the best results for you. And you'll be better prepared to talk with your care team.

Don't know what to ask? You're not alone. That's why we include suggested questions to ask at the end of chapters.

Keep reading to find the best care for you.

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Side effects of CAR T-cell therapy

9 How does CAR T-cell therapy work?

10 What is the process of CAR T-cell therapy?

12 Side effects of therapy

14 Key points

14 Questions to ask

CAR T-cell therapy alters your immune cells so they can attack cancer cells. It may cause unwanted health issues as it's attacking the cancer. Many of these issues can be treated, and some can even be prevented.

Like other cancer treatments, CAR T-cell therapy can cause side effects. This chapter explains several side effects that can be caused by any CAR T-cell therapy. Before learning about these side effects, it may be helpful to first review some basics about CAR T-cell therapy.

How does CAR T-cell therapy work?

To understand how CAR T-cell therapy works, it's important to know what CAR T cells are. CAR T cells are made in a lab, using the T cells made in, and taken out of, the body's immune system.

CAR T-cell therapy works by changing your immune cells (T cells) in a way that makes it easier for them to find and kill cancer cells. It's used to treat cancer that didn't respond to other treatment or that has come back after being treated.

CAR T-cell therapies approved by the FDA to treat cancer are listed in **Guide 1**.

Guide 1
Types of cancer and their CAR T-cell therapies

Type of cancer	Name of treatment (generic/brand)
B-cell leukemias and lymphomas	Axicabtagene ciloleucel (Yescarta) Brexucabtagene autoleucel (Tecartus) Lisocabtagene maraleucel (Breyanzi) Obecabtagene autoleucel (Aucatzyl) Tisagenlecleucel (Kymriah)
Multiple myeloma	Ciltacabtagene autoleucel (Carvykti) Idecabtagene vicleucel (Abecma)

Anti-CD19 therapy

The CAR T-cell therapies used to treat certain blood cancers, including some forms of lymphoma, leukemia, and multiple myeloma, target the antigen CD19.

Anti-BCMA therapy

The CAR T-cell therapies used to treat multiple myeloma target B-cell maturation antigen, or BCMA. They're called anti-BCMA CAR T-cell therapies. The way these therapies work is discussed in *Chapter 3: Side effects of anti-BCMA CAR T-cell therapy*.

In addition to the side effects discussed in this chapter, there are some that only affect people being treated with anti-BCMAs. These side effects are also discussed in Chapter 3.

What is the process of CAR T-cell therapy?

If you haven't had CAR T-cell therapy, here is what to expect.

1. First, blood is removed from your arm.
2. White blood cells called T cells are taken out of your blood. This can take several hours. (It may need to be repeated another day to get enough T cells.) Your blood is then sent to a lab.
3. At the lab, a gene is added to the T cells to make CAR T cells. They multiply to create enough cells to kill the cancer cells in your body. This can take several weeks.
4. A few days before treatment, you will likely have a short course of chemotherapy to prepare your body to receive the altered cells.
5. The CAR T cells are put back (infused) into the blood. The infusion usually takes up to an hour.
6. CAR guides the T cells to find and kill cancer cells.
7. You will be monitored closely for side effects for at least 1 month and up to 6 months.

Before infusion

Before CAR T-cell infusion, your care team will do what's needed to prepare your body. This includes baseline (starting) tests and possibly giving you medicine to help prevent side effects.

For an overview of what will happen before therapy, see **Guide 2**.

Guide 2
Before CAR T-cell infusion

You will have:	Central venous catheter placement Heart check Neurological exam Blood tests
You may have:	Echocardiogram (ECG) MRI Medicine to prevent: • Tumor lysis syndrome • Seizures

Before your infusion, you will have:

- Placement of a **central venous catheter**. A thin tube is inserted into your vein, usually below the collarbone or in the upper arm. The tube is guided into a large vein above the right side of the heart. When needed, this catheter will be accessed to draw blood, give fluids or medicines, or put CAR T cells into your blood.
- **A heart check**. This may include an ultrasound of your heart (echocardiogram, or ECG). This noninvasive test is performed using a handheld wand placed on your chest. If you have a history of heart problems, your doctor will consult a heart expert (cardiologist).
- **A neurological (neuro) exam** to check how well your brain and nerves are working. You may also have an MRI of your brain. Some CAR T-cell therapies are more likely to cause nervous system side effects than others. To learn more, see *Chapter 6: ICANS*.
- **Blood tests** to measure certain proteins that will tell your health care team if you are at high risk for blood issues. They will also check for certain viruses, including HIV and viruses that affect the liver.

  Ongoing blood testing will be ordered to check protein levels, blood cell counts, and how well your:

  - Blood is clotting
  - Liver and kidneys are working

Echocardiogram

Before CAR T-cell therapy, your heart will be checked. This may include an echocardiogram.



Preventive medicine you may be given

Before infusion, you may be given medicine to prevent:

- **Tumor lysis syndrome**. This syndrome occurs when harmful contents of dying cancer cells enter the bloodstream. It can lead to organ damage, can be life-threatening, and most often occurs after treatment of large tumors or fast-growing cancers. Medicines given may include:
  - Allopurinol (Aloprim)
  - Febuxostat (Uloric)
  - Rasburicase (Elitek)
- **Seizures**. Levetiracetam is often given on the day of infusion if you are at high risk for certain side effects of the nervous system, such as seizures. The drug is usually given orally (by mouth), and you will continue to receive it every 12 hours for up to a month.

After CAR T-cell infusion

Expect to stay at or near the hospital after infusion. This allows for close monitoring and treatment of serious side effects, which will be discussed in the next section.

If hospital (inpatient) care isn't needed, close monitoring by a center with CAR T-cell experience may be an option. At the first sign of side effects of the brain or nervous system, hospitalization is needed.

After leaving the hospital, you will continue to be closely monitored for side effects for at least 1 month after infusion, and possibly up to 6 months. This depends on the CAR T-cell product you received (see **Guide 1**).

Your care team will instruct you not to drive or do anything else potentially dangerous for at least 2 weeks after the infusion.

Side effects of therapy

CAR T-cell therapy side effects include:

- Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), which is hyperinflammation
- IEC-associated hematotoxicity (ICAHT), which is low blood counts
- B-cell aplasia
- Infections
- Low immunoglobulin

Hyperinflammation

A possible side effect when immune cytokines are over-produced is hyperinflammation. This is called IEC-HS.

Your care team will monitor for IEC-HS. It tends to occur in people who have already had treatment for CRS (see Chapter 5). Signs and symptoms include:

- High iron levels
- Low blood cell counts
- Blood clotting problems
- High liver enzyme levels
- Organ damage and failure

The 2 most common side effects of CAR T-cell therapy are:

Cytokine release syndrome

and

Immune effector cell-associated neurotoxicity syndrome

Low blood counts

Your levels of red and white blood cells and platelets may be lower than normal for weeks to months after CAR T-cell infusion. This is called ICAHT.

These treatments for ICAHT may be used as needed:

- **Blood transfusions**. In a transfusion, cells donated by healthy volunteers are put into your bloodstream through a vein. Transfusions can raise red blood cell or platelet counts.
- **Growth factor therapy**. These medicines help bone marrow make more blood cells. It's given by infusion or intravenously.
  - Stem cell boosts, if available, may be used if transfusions and growth factor treatments don't raise blood cell counts. There isn't much information available at this time, though, about how well this treatment works.

B-cell aplasia

In the process of killing cancer cells, normal B cells are also destroyed. Absence of B cells is called B-cell aplasia. It can last a long time. Having too few B cells can mean that the CAR T cells continue to fight cancer. But it also means that you have fewer immune cells to protect you from infection.

Infections

Since these therapies affect the immune system, they can make it hard for the body to fight infection. Two infections that can happen as a side effect of CAR T-cell therapy include:

- Fungal infection of the lungs (*Pneumocystis jiroveci* pneumonia)
- Chickenpox and shingles (caused by the varicella zoster virus)

Medicine to prevent these infections is recommended for at least 6 months after CAR T-cell treatment.

Low immunoglobulin

Immunoglobulin (Ig) is a protein that helps fight infection. Levels of this protein can become low in people being treated with immunotherapy.

B-cell lymphomas or leukemias

Ig replacement, given monthly by IV or weekly under the skin, may be given to people who've received CAR T-cell therapy and have had both of these:

- Very low Ig levels
- Serious or frequent infections, especially of the airways

Ig replacement may be used to maintain Ig levels high enough to reduce the risk for infections or until infections have stopped.

Multiple myeloma

For people being treated with anti-BCMA CAR T-cell therapy, Ig replacement therapy may be given by IV for people who have very low levels of Ig before starting anti-BCMA CAR T-cell therapy.

Key points

- CAR T-cell therapy works by changing your own immune cells (T cells) in a way that makes it easier for them to find and kill cancer cells.
- Before infusion, you may be given medicine to prevent tumor lysis syndrome and seizures.
- The 2 most common side effects are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
- Medicine to prevent certain infections is recommended for at least 6 months after CAR T-cell treatment.
- Your care team will monitor you for low blood cell counts, B-cell aplasia, and low immunoglobulin (Ig).

Questions to ask

- What is the name of the CAR T-cell therapy I am taking?
- What are common side effects of that therapy?
- How are those side effects prevented or treated?
- Will I be given medicine to help fight infection?

What's next

In the next chapter, you will learn more about the side effects of anti-BCMA therapy, a unique CAR T-cell therapy used to treat multiple myeloma.

3

Side effects of anti-BCMA CAR T-cell therapy

16 Side effects of therapy

17 Nervous system side effects

19 IEC-associated enterocolitis

19 Low immunoglobulin

20 Key points

20 Questions to ask

Anti-B-cell maturation antigen (BCMA) CAR T-cell therapies are designed to treat multiple myeloma. This chapter explains side effects that affect the brain and nerves, as well as the digestive and immune systems.

Anti-BCMA CAR T-cell therapies target B-cell maturation antigen (BCMA). This antigen is found mostly on multiple myeloma cells. Anti-BCMA CAR T-cell therapies are:

- Idecabtagene vicleucel (Abecma)
- Ciltacabtagene autoleucel (Carvykti)

"I've learned over the years not to gloss over anything that's going on in my body whenever I meet with my doctors."



Side effects of therapy

The 2 most common side effects of anti-BCMA therapy are:

- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)

These side effects can also occur with other types of immunotherapy, so they're discussed in Chapter 5 and Chapter 6.

Side effects common to all CAR T-cell therapies are explained in Chapter 2. Side effects caused by anti-BCMA CAR T-cell therapies are addressed in this chapter. They are:

- Nervous system conditions
- Inflammation of the intestines
- Low number of antibodies, also called immunoglobulins (Ig), which help fight infections

Your health care team will manage side effects according to recommendations made by both of the following:

- Makers of the anti-BCMA therapy being used
- The health care center where you're being treated

Nervous system side effects

Anti-BCMA CAR T-cell therapy can cause nervous system side effects that are different from ICANS side effects. They are:

- Immune effector cell (IEC)-associated Parkinsonism
- IEC-associated cranial nerve palsy
- IEC-associated polyradiculoneuritis

Compared to ICANS, these issues start late. Symptoms typically begin between 11 and 108 days (about 3.5 months) after infusion.

IEC-associated Parkinsonism

IEC-associated Parkinsonism is a side effect of anti-BCMA therapies. As its name suggests, symptoms are like those caused by Parkinson's disease. Possible symptoms are listed in **Guide 3**.

Risk factors

Risk factors for IEC-associated Parkinsonism are:

- A large amount of cancer in the body before treatment is started
- Severe, early CRS
- A history of ICANS
- CAR T cells that have persisted in the body beyond their expected time

Guide 3
IEC-associated Parkinsonism symptoms

Moving slowly	Personality changes
Stiffness	Slow thinking
Changes in how you walk	Impaired memory
Shaking (tremor)	Trouble balancing
Weak voice	Trouble with facial expressions (smiling, raising eyebrows)

Managing IEC-associated Parkinsonism

For mild symptoms, you may receive an oral steroid (dexamethasone) for 3 to 5 days.

If symptoms are severe, don't go away after treatment, or come back and a high level of CAR T cells is found in your blood, you may be given a strong dose of cyclophosphamide (Cytoxan), a type of chemotherapy.

Treating these side effects may include chemotherapy given by a needle into your spine (lumbar puncture) or ruxolitinib, a type of targeted therapy that regulates blood cell production and inflammation.

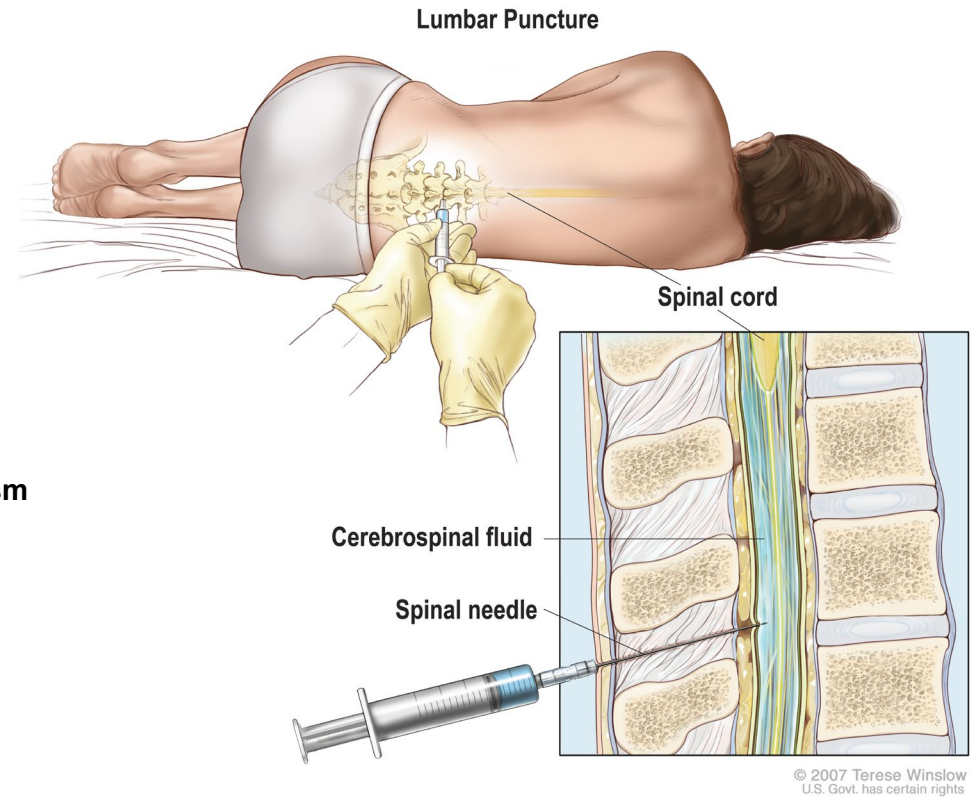
Keep in mind: There isn't much research on treatment for IEC-associated Parkinsonism. Medicine used to treat Parkinson's disease has not been effective for IEC-associated Parkinsonism. Your care team will weigh the possible benefits of using these therapies with the risks. Infection is one of the risks.

IEC-associated cranial nerve palsy and IEC-associated polyradiculoneuritis

IEC-associated cranial nerve palsy is a condition that causes weakness or trouble moving parts of the head and face and upper body.

IEC-associated polyradiculoneuritis is when certain nerves become inflamed.

Chemotherapy can be given directly into the spinal fluid if IEC-associated Parkinsonism becomes severe.



Possible symptoms are found in **Guide 4**.

Managing IEC-associated cranial nerve palsy and IEC-associated polyradiculoneuritis

For mild symptoms (such as weakness on one side of your face), you'll be given steroids (prednisone) for 7 to 10 days.

For severe symptoms (such as weakness on both sides of your face or sudden weakness of legs and arms), you may be given intravenous Ig (IVIg) therapy (explained later in this chapter).

IEC-associated enterocolitis

Enterocolitis is when the small intestine and colon (part of the large intestine) become inflamed. The intestines help you digest food. Diarrhea (that does not have blood in it) that comes on quickly about 1 to 3 months after CAR T-cell infusion is the most common symptom of IEC-associated enterocolitis.

Guide 4
Symptoms of nerve weakness and damage

Facial weakness or trouble moving facial muscles
Numbness, especially of the hands and feet
Tingling or pain
Trouble balancing
Muscle weakness or trouble moving hands, feet, or arms

Planning treatment

If your care team thinks you may have IEC-associated enterocolitis, you'll get:

- Tests for certain viruses and bacteria (like *C. diff*, or *Clostridioides difficile*, a highly contagious bacterial infection)
- A colonoscopy with tests of tissue samples

You'll be treated for IEC-associated enterocolitis if testing and colonoscopy show you:

- Do not have an infection
- Have inflammation throughout your small intestine and colon
- Have certain white blood cells (lymphocytes) in the lining of your small intestine

Medicine used for treatment

A steroid will be given right away. If the steroid doesn't help or diarrhea doesn't stop when the steroid is tapered, treatment may include 1 of these medicines used to treat inflammation:

- Infliximab (Remicade)
- Vedolizumab (Entyvio)

These medicines may be used with, or instead of, steroids.

Low immunoglobulin

IVIg is given to people who have very low levels of Ig before they start anti-BCMA CAR T-cell therapy.

Key points

- Anti-BCMA CAR T-cell therapies are idecabtagene vicleucel (Abecma) and ciltacabtagene autoleucel (Carvykti).
- Anti-BCMA side effects can affect the brain and nerves, as well as the digestive system.
- Nervous system side effects are IEC-Parkinsonism, IEC-associated cranial nerve palsy, and IEC-associated polyradiculoneuritis. Symptoms include pain; weakness of the face, hands, and feet; numbness; and trouble walking and balancing.
- The main symptom of IEC-associated enterocolitis is diarrhea that comes on quickly.
- Steroids are typically used to treat anti-BCMA side effects.

Questions to ask

- Which anti-BCMA CAR T-cell therapy will I be given?
- Are there specific side effects associated with that therapy?
- How will my side effects be treated?
- Who should I contact if I notice symptoms?

What's next

In the next chapter, you will learn about lymphocyte engager therapy, another kind of immunotherapy that's sometimes used to treat multiple myeloma. Possible side effects, and how they're managed, will be discussed.

4

Side effects of lymphocyte engager therapy

22 How does lymphocyte engager therapy work?

23 Side effects of therapy

24 Managing side effects

25 Key points

25 Questions to ask

Lymphocyte engager therapy helps your white blood cells connect to and destroy cancer cells. Management of side effects is based on the type of cancer and other factors.

Guide 5
Types of cancer and their lymphocyte engager therapies

Type of cancer	Generic name of treatment (brand)
B-cell acute lymphoblastic leukemia	Elranatamab-bcmm (Elrexfio) Talquetamab-tgvs (Talvey) Teclistamab-cqyv (Tecvayli) Linvoseltamab-gcpt (Lynozyfic)
B-cell lymphomas	Epcoritamab-bysp (Epkinly) Glofitamab-gxbm (Columvi) Mosunetuzumab-axgb (Lunsumio)
Small cell lung cancer	Tarlatamab-dlle (Imdelltra)
Uveal melanoma	Tebentafusp-tebn (Kimmtrak)

Like many cancer treatments, lymphocyte engager therapy can cause side effects. In this chapter, you will learn about lymphocyte engager therapy, its side effects, and how these side effects are managed.

How does lymphocyte engager therapy work?

To understand how lymphocyte engager therapy works, it's important to know what lymphocytes are. Lymphocytes are white blood cells made in the immune system. They're made of T cells and B cells.

Lymphocyte engager therapy works by connecting lymphocytes with cancer cells. When they connect—or engage—the 2 kinds of cells make it easier for the immune system to find and kill cancer.

Lymphocyte engager therapy is used to treat certain cancers that didn't respond to other treatments, or that have come back after treatment. This includes:

- Some forms of lymphoma, leukemia, and multiple myeloma
- One kind of lung cancer
- A certain cancer of the eye

The therapies approved by the FDA to treat cancer are given in **Guide 5**.

Side effects of therapy

The 2 most common side effects of lymphocyte engager therapies are:

- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)

These side effects can also occur with other types of immunotherapy, so they're discussed in Chapter 5 and Chapter 6.

Other common side effects of lymphocyte engager therapies are listed in **Guide 6**. Here are some more important things to know about the side effects of these therapies:

- Each lymphocyte engager has its own unique common side effects.
- If side effects are mild, your treatment may be paused until they get better. Your care team will likely start treatment again, possibly at a lower dose.

Guide 6
Common side effects of lymphocyte engager therapy

Generic treatment	Low immuno-globulin	Tumor lysis syndrome	High liver enzymes	Altered taste	Rash	Other*
Blinatumomab	●	●	●			
Elranatamab	●					
Talquetamab	●			●		
Teclistamab	●					●
Linvoseltamab	●					●
Epcoritamab	●					
Glofitamab	●					
Mosunetuzumab	●					
Tarlatamab				●		
Tebentafusp			●		●	

*Muscle and joint pain, fatigue, nausea, headaches, and shortness of breath.

Side effects include:

- Tumor lysis syndrome, when harmful contents of dying cancer cells enter the bloodstream. It can lead to organ damage and be life-threatening. It most often occurs after treatment of large tumors or fast-growing cancers.
- Low immunoglobulin (Ig) levels, which makes it hard for your body to fight infection.
- High liver enzymes, a sign of a problem with the liver.
- Altered taste, rash, muscle and joint pain, fatigue (extreme tiredness), nausea, headaches, and shortness of breath.

Managing side effects

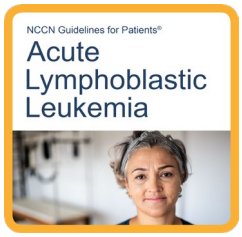
Side effects are managed according to recommendations for each cancer type, the lymphocyte engager product, and clinical trial practices.

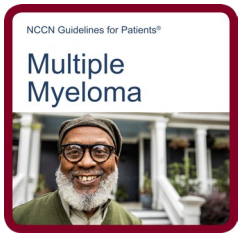
For B-cell acute lymphoblastic leukemia and multiple myeloma

If you're having therapy that treats:

- **B-cell acute lymphoblastic leukemia**, your care team will make decisions about managing side effects based on *NCCN Guidelines for Patients: Acute Lymphoblastic Leukemia*.
- **Multiple myeloma**, your care team will make decisions about managing side effects based on *NCCN Guidelines for Patients: Multiple Myeloma*.

More information on treatments for these two types of blood cancers is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.





For B-cell lymphomas and small cell lung cancer

- You may be given an antibiotic (fluoroquinolone) and an antifungal (fluconazole) medicine if your white blood cells are low.
- You may also be given certain growth factor medicines to help your body make more white blood cells.

For B-cell lymphomas only

- Medicine to prevent a fungal lung infection
- Medicine to prevent the virus that causes chickenpox and shingles

Your team will also check your Ig levels on a regular basis. If you have infections that don't go away, keep happening, or are severe in addition to low levels of Ig, you may be given Ig replacement therapy.

Low white blood cells, or neutropenia, make it harder for your body to fight infection.

Key points

- Lymphocyte engager therapy works by connecting immune cells with cancer cells.
- It's used to treat some forms of lymphoma, leukemia, and multiple myeloma, one kind of lung cancer, and a certain cancer of the eye.
- The 2 most common side effects are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
- Having low levels of immunoglobulin (Ig) is a common side effect of several lymphocyte engager therapies.
- Other side effects include tumor lysis syndrome, high liver enzymes, altered taste, and rash.

Questions to ask

- What is the name of the lymphocyte engager therapy I am taking?
- What are common side effects of that therapy?
- How are those side effects treated?

What's next

In the next chapter, you'll read about CRS, one of the most common side effects of CAR T-cell therapy and lymphocyte engager therapy. CRS can be severe. You'll learn about how serious side effects are managed.

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Cytokine release syndrome

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Cytokine release syndrome (CRS) is a common side effect of CAR T-cell therapy and lymphocyte engager therapy. Although CRS is often mild, it can be severe.

Cytokine release syndrome (CRS) is more common with CAR T-cell therapy than with lymphocyte engager therapy. In this chapter, you'll read about CRS, its signs and symptoms, the serious issues it can cause, and how it's managed. You'll also learn how CRS due to lymphocyte engager therapy is different from CRS due to CAR T-cell therapy.

What is CRS?

CRS is when immune cells affected by CAR T-cell or lymphocyte engager therapy release many inflammation-causing cytokines into the blood. Cytokines are proteins that carry out different immune-related jobs in the body. This causes your immune system to go into overdrive.

Signs and symptoms of CRS are listed in **Guide 7**.

CRS usually starts 1 to 3 days after lymphocyte engager infusion and 2 to 3 days after CAR T-cell infusion. However, it can start as soon as hours after infusion and as late as 10 to 15 days afterward. The syndrome usually lasts about a week.

CRS can lead to damage of major organs. The heart, liver, kidneys, and lungs may be affected. How much cancer is in your body and the specific medicine you are treated with play a role in how likely you are to get CRS.

How severe is it?

A grading system helps determine how severe the CRS is. Determining the severity helps guide treatment decisions.

A person with a fever has grade 1, or mild, CRS. If low blood pressure, low oxygen, or both problems develop, the CRS grade gets higher. Grade 4 CRS is when:

- Blood pressure becomes dangerously low and requires very aggressive support
- Oxygen becomes severely low
- Or both

Guide 7
CRS signs and symptoms

Fever
Low blood pressure
Low tissue oxygen levels
Chills
Rapid heartbeat
Trouble breathing

Serious signs and symptoms

CRS is mild for most people, but serious and possibly deadly problems are possible. The serious problems are described next.

Low blood pressure. Blood pressure is the strength of blood pushing against the sides of blood vessels. Low blood pressure (hypotension) is dangerous. It reduces blood flow to the heart, brain, and other vital organs. In severe cases, low blood pressure can be life-threatening.

Severely low blood pressure is treated with vasopressors. These medicines raise blood pressure by contracting (tightening) blood vessels.

Lack of oxygen to tissues. Hypoxia is a dangerous condition. It happens when not enough oxygen reaches the cells and tissues of the body. The brain, liver, and other organs can be damaged in minutes if they don't get enough oxygen.

Oxygen therapy may be given through noninvasive nose tubes or a mask that covers your nose and mouth. The method used to give oxygen depends on how low the level is.

In severe cases, intubation may be needed. Intubation means a tube is put through the mouth and into the airway. The tube is connected to a respirator that moves air in and out of your lungs. This is called mechanical ventilation.



What's the difference between a sign and a symptom of a health condition?

Signs are found using medical tests and tools (stethoscope, thermometer, pulse oximeter).

Symptoms are things we feel like nausea, headaches, and pain.

Effects on the heart. CRS can cause changes in the way the heart beats and affect how well the heart works.

These are some of the ways your heart can be affected by CRS:

- Atrial fibrillation (A-fib). Fast, irregular heartbeat
- Ventricular tachycardia (V-tach). Heart beats quickly but regularly
- Heart failure. Heart doesn't pump enough blood for your body's needs
- Cardiac arrest. Causes you to stop breathing and pass out

Changes in heartbeat can be dangerous. Extra medicines and other treatments may be needed. Cardiac arrest is rare but can be life-threatening.

Poor kidney function. CRS can cause the kidneys to suddenly stop filtering waste from the blood. This is called acute kidney injury (AKI). It is not common. If it occurs, the effects are usually reversible (not permanent).

Capillary leak syndrome. This is a condition in which fluid and proteins leak out of the bloodstream through tiny blood vessels (capillaries). It can lead to dangerously low blood pressure, organ failure, and shock. Shock is a life-threatening problem. It occurs when there's a sudden drop in blood flow in the body.

CRS management

Treatments for CRS include steroids and interleukin (IL) blockers. These medicines, described in this section, are given intravenously.

The treatments for CRS related to CAR T-cell therapy and to lymphocyte engager therapy are similar.

Steroids and tocilizumab

Steroids are often used together with tocilizumab (Actemra) to treat severe CRS. They may also be used to treat milder (grade 1) CRS in certain cases.

- Steroids reduce the activity of the immune system. They're also used to treat more severe neurological side effects. Dexamethasone and methylprednisolone are commonly used steroids.
- Tocilizumab is a prescription medicine that blocks interaction between IL-6 and its receptors. IL-6 is a cytokine (a small protein) released during CRS. This leads to very high levels of it in the blood.

Anakinra and siltuximab

For severe CRS that doesn't improve with tocilizumab and high-dose steroids, treatment with anakinra (Kineret) may be given. Anakinra blocks the activity of IL-1, a cytokine that causes inflammation.

Siltuximab (Sylvant) is another IL-6 blocker that may be used to treat severe lymphocyte engager-related CRS that doesn't respond to tocilizumab and steroids alone.

Other things to know about managing CRS

CRS is often treated in the hospital so you can be closely watched and managed. However, some people with CRS can be monitored at outpatient centers. Outpatient care may be an option if a center is very close to the hospital and if the staff has experience in managing CRS.

Management may also include:

- IV hydration
- Antibiotics for people with neutropenia (low white blood cells)

CRS related to CAR T-cell therapy

If you have signs and symptoms of CRS, your care team will check to see if you have an infection or if your cancer has progressed. If they rule out those issues, they'll treat CRS quickly to keep the syndrome from getting worse.

Tests and treatment

Your care team will check for sepsis, a very serious immune response to infection. Sepsis is treated with antibiotics.

You may also be given certain growth factor medicines to help your body make more white blood cells, if they're low. Low white blood cells make it harder for your body to fight infection.

Tests you may have

You may have an echocardiogram (ECG) and other tests to monitor how well your blood is circulating and how well your heart is working. If your heart is beating too quickly (V-tach) even after standard treatment, you may have:

- An ECG to measure the heart's activity
- Blood tests for certain proteins in your blood, which may mean your heart is damaged

Treatment for severe CRS

If CRS is severe and doesn't improve after the treatments explained in this chapter, you may be treated with:

- Ruxolitinib (Jakafi), a targeted therapy
- Cyclophosphamide (Cytoxan), a chemotherapy treatment
- Intravenous immunoglobulin
- Anti-thymocyte globulin (Atgam), an immunosuppressant
- Dasatinib (Sprycel), a targeted therapy
- Chemotherapy injected into the spinal fluid
- Blood-filtering therapies

Keep in mind: Experience with the treatments listed for severe CRS is limited. Your care team will weigh possible side effects, such as infection risk, with potential benefits.

CRS related to lymphocyte engager therapy

Risk factors

Severe CRS with lymphocyte engager therapy is very rare. And the syndrome is less common in people undergoing lymphocyte engager therapy than in those receiving CAR T-cell therapy.

Some people who have treatment with lymphocyte engagers are more likely to develop severe CRS or have trouble managing it. See risk factors in **Guide 8**.

Guide 8
Severe CRS risk factors: lymphocyte engagers

You have a high amount of cancer in the body
Cancer has: • Grown • Spread (metastasized) • Gotten worse quickly
Blood tests show signs of inflammation
You are older and have difficulty taking care of yourself
You have other diseases or medical conditions
CRS has happened quickly (less than 4 hours after start of infusion)

Tests and treatment

If you have lymphocyte engager-related CRS, you'll have blood and urine tests and a chest x-ray.

Your heart may be monitored and you may have an echocardiogram (heart ultrasound) if CRS is severe.

In addition to the treatments explained earlier in this chapter, management for CRS related to lymphocyte-engagers includes:

- Acetaminophen (Tylenol)
- Cooling blanket
- Managing heat-related illness

Key points

- CRS is the release of inflammation-causing cytokines into the blood after an infusion of CAR T-cell therapy or lymphocyte engager therapy.
- It's the most common, serious side effect of CAR T-cell therapy and lymphocyte engager therapy.
- CRS is more common in people treated with CAR T-cell therapy than in those treated with lymphocyte engager therapy.
- Signs and symptoms include fever, low blood pressure, low tissue oxygen, chills, rapid heartbeat, and trouble breathing.
- Serious CRS issues include heart problems, acute kidney injury, and capillary leak syndrome.
- Steroids are typically used together with tocilizumab (a drug that blocks a cytokine released during CRS) to treat this syndrome.
- Anakinra may be used to treat severe CRS that doesn't improve with other treatment.

Questions to ask

- What is the name of the therapy I am taking?
- Is it a CAR T-cell therapy or a lymphocyte engager therapy?
- What side effects are specific to the therapy?
- How are they treated?

What's next

In Chapter 6, you'll read about ICANS. ICANS is another common side effect of CAR T-cell and lymphocyte engager immunotherapies.

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36 ICANS management

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38 Questions to ask

Nervous system side effects are common with CAR T-cell therapy and lymphocyte engager therapy. These symptoms are called immune effector cell-associated neurotoxicity syndrome (ICANS). It affects the brain, spinal cord, and nerves. Although symptoms are usually mild, very serious problems can occur.

In this chapter, you'll read about nervous system side effects, the serious issues they can cause, and how they're managed. You'll also learn how nervous system side effects due to lymphocyte engager therapy differ from CRS due to CAR T-cell therapy.

What is ICANS?

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a term used to describe some (but not all) side effects of the nervous system caused by CAR T-cell and lymphocyte engager therapies.

Neurotoxicity means damage to the nervous system. The nervous system includes the brain, spinal cord, and nerves. This complex system controls everything the body does. Movement, sensation, and breathing are all guided by the nervous system. It is the hub of thinking, memory, and learning.

Symptoms of damage to the nervous system are listed in **Guide 9**.

Nervous system side effects, if they occur, typically start 4 to 10 days after infusion. They may come and go. You'll be seen by a neurologist (an expert in nervous system conditions) right away if you have signs of neurotoxicity.

These side effects are usually reversible if treated right away.

Guide 9 **Nervous system side effects of CAR T-cell therapies**
Headache
Memory issues
Dizziness
Anxiety
Trouble sleeping
Trouble finding words or speaking, understanding speech, or both
Shaking
Feeling very sleepy
Confusion
Trouble with balance, walking, or both
Impaired state of reality (psychosis)
Sudden twitching or jerking

How severe is it?

Two tests are used together to determine the severity of ICANS. Determining the severity helps guide treatment decisions. The tests are:

1. A snapshot of your mental state using the Immune Effector Cell-Associated Encephalopathy tool. This tool measures your ability to carry out simple tasks, such as writing and counting. A score of 0 (emergency) to 10 (mild) is possible.
2. A point system developed by the American Society for Transplantation and Cellular Therapy. It's used to assign ICANS a grade from 1 (mild) to 4 (life-threatening). It measures:
   - How alert or responsive you are
   - If you are having seizures
   - If you have severe muscle weakness
   - If there is swelling of your brain

Serious symptoms of ICANS

In more severe cases, seizures, brain swelling, coma, and trouble moving can occur. These may be life-threatening. These and other possible symptoms are described next.

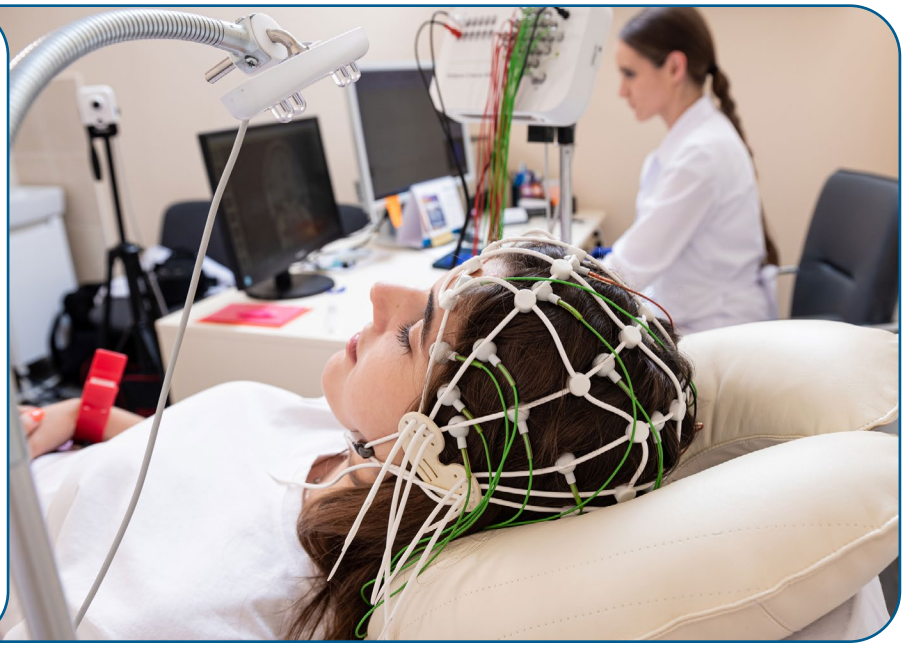
- **Seizures**. Abnormal electrical signals in the brain cause sudden and uncontrolled body movements. Shaking is common. Other symptoms include behavior changes, loss of awareness, and loss of muscle control.

  A seizure that lasts more than 5 minutes, or many seizures in a row, is a medical emergency.

Brain swelling. Increased pressure inside of the skull. Lumbar puncture can help relieve this pressure. Brain swelling is a very rare side effect.

Monitoring for seizures

You may have an electroencephalogram (EEG) to monitor for seizures during ICANS. An EEG is a recording of electrical activity in the brain.



Coma. A deep unconscious state. A coma is a medical emergency. A person in a coma doesn't respond to their surroundings or wake up by normal means.

Trouble moving. Not being able to move your legs or the muscles on one side of your body are symptoms of damage to the brain or nerves.

ICANS management

Since lymphocyte engager therapy is given in multiple sessions, your care team may pause therapy if you develop ICANS. They will decide whether to continue or pause therapy based on the type of you therapy you are receiving and how severe the side effects are. If ICANS is very severe, they may stop the therapy.

Tests you may have

Tests you may have in the hospital are:

- **Neurological exams** mentioned earlier in this chapter. You'll be seen by a neurologist, an expert in these kinds of conditions.
- **Electroencephalogram (EEG)** to track and record brain wave patterns. The patterns are relayed by small metal sensors placed on your scalp.
- **Brain imaging** to look for swelling or damage. You may have an MRI of your brain, with and without contrast. If MRI isn't possible, you may have a CT scan instead. Contrast is used to enhance the images.

Read on to learn how ICANS is managed.

MRI of the brain

This imaging test is used to learn if there is swelling of, or damage to, the brain.



Mild side effects

Your care team will treat your side effects right away so ICANS doesn't get worse. Supportive care is often all that's needed. Supportive care includes:

- Giving fluids intravenously (an IV drip) to keep you hydrated.
- Monitoring electrolytes (minerals that help keep your body working properly). Giving supplements if needed.
- Taking steps to prevent food or liquids from going into your airways (called aspiration). This can lead to infection (often pneumonia) and inflamed lungs.

Steroids (oral or IV) may also be used for mild ICANS. Dexamethasone and methylprednisolone are widely used steroids.

Moderate or severe side effects

Steroids are given through a vein. Additional medicine may be used.

For CAR T-cell-related ICANS:

- Anakinra may be added for severe ICANS that isn't improving with high-dose steroids.
- Tocilizumab may be given if CRS is also happening at the same time.

See *Chapter 5: Cytokine release syndrome* for more information on tocilizumab and anakinra.

For lymphocyte engager-related ICANS:

- **Levetiracetam** (Keppra) may be prescribed. It may also be given for milder ICANS. Levetiracetam is used to treat seizures.
- **Lumbar puncture** is a simple bedside procedure. It's used to remove a sample of spinal fluid that flows in and around the brain and spinal cord for testing.

Key points

- Nervous system side effects of CAR T-cell and lymphocyte engager therapies are called neurotoxicities.
- They include immune effector cell-associated neurotoxicity syndrome (ICANS) and some other symptoms.
- ICANS is more common in people treated with CAR T-cell therapy than in those treated with lymphocyte engager therapy.
- Symptoms include headache, dizziness, trouble sleeping, and trouble speaking.
- Serious side effects include seizures, brain swelling, coma, and trouble moving.
- For mild nervous system side effects, only supportive care may be needed.
- Steroids and other medicines may be necessary to treat moderate to severe side effects.

Questions to ask

- What is the name of the therapy I am taking?
- Is it a CAR T-cell therapy or a lymphocyte engager therapy?
- What side effects are specific to the therapy?
- How are those side effects treated?

What's next

It's common to have questions about the type of treatment you are receiving and how side effects may affect your life. In the next chapter, you can find other resources that might be helpful to you.



Take our survey and help make the NCCN Guidelines for Patients better for everyone!

NCCN.org/patients/comments

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Other resources

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Want to learn more? Here's how you can get additional help.

What else to know

This guide helps you know your options so you can make informed decisions and improve your cancer care. But it's not the only resource that you have.

Ask for as much information and help as you need. Many people are interested in learning more about:

- The specific immunotherapy they're being treated with
- Ways to manage mild symptoms
- Managing fear and anxiety about immunotherapy and possible side effects
- How to talk to the people who support you about the kind of help you need
- Fertility and family planning

What else to do

Your health care center can help you with next steps. It often has on-site resources to help meet your needs and find answers to your questions. Health care centers can also inform you of resources in your community.

Where to get help

Look through the list below and visit the provided websites to learn more about these organizations.

Blood Cancer United
bloodcancerunited.org

BMT InfoNet (Blood & Marrow Transplant Information)
bmtinfonet.org

Bone Marrow and Cancer Foundation
bonemarrow.org

Cancer*Care*
cancercare.org

Cancer Hope Network
cancerhopenetwork.org

GRACE
cancergrace.org

Imerman Angels
imermanangels.org

Lymphoma Research Foundation
lymphoma.org

National Bone Marrow Transplant Link
nbmtlink.org

National LeioMyoSarcoma Foundation
nlmsf.org

NMDP
nmdp.org

Save Your Skin Foundation
saveyourskin.ca

Triage Cancer
triagecancer.org

Questions to ask

- Who can I talk to about housing, food, and other basic needs?
- What help is available for childcare and home care?
- How can I connect with others and build a support system?
- Who can I talk to if I don't feel safe at home, at work, or in my neighborhood?



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



Words to know

B-cell aplasia
Having low numbers of B cells. A common and sometimes long-term side effect of CAR T-cell therapy.

B-cell maturation antigen (BCMA)
An antigen found on multiple myeloma cells.

capillary leak syndrome
The escape of fluid and proteins from blood vessels into surrounding tissues. May result in dangerously low blood pressure.

chimeric antigen receptor (CAR) T-cell therapy
A type of immunotherapy in which T cells (a type of immune system cell) are modified in a way that allows them to find and kill cancer cells.

cytokine release syndrome (CRS)
A potentially serious side effect of CAR T-cell therapy. Caused by the release of inflammatory proteins into the blood from immune cells affected by the immunotherapy.

hypotension
Low blood pressure. A possible complication of cytokine release syndrome.

hypoxia
Decreased oxygen reaching body tissue. A possible complication of cytokine release syndrome.

immune effector cell (IEC)
A type of immune cell that fights threats in the body.

immune effector cell (IEC)-associated cranial nerve palsy
A possible side effect of anti-BCMA CAR T-cell therapy. Causes weakness or trouble moving parts of the head, face, and upper body.

immune effector cell (IEC)-associated enterocolitis
Inflammation of the small intestine and colon (part of the large intestine). A possible side effect of anti-BCMA CAR T-cell therapy.

immune effector cell-associated hematotoxicity (ICAHT)
A CAR T-cell therapy that affects blood counts.

immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS)
A serious side effect in which the body makes too many of a type of white blood cell and T cell, causing hyperinflammation. Previously known as macrophage activation syndrome.

immune effector cell-associated neurotoxicity syndrome (ICANS)
A group of nervous system-related side effects of CAR T-cell therapy.

immune effector cell (IEC)-associated Parkinsonism
A possible side effect of anti-BCMA CAR T-cell therapy. Symptoms are like those of Parkinson's disease, including problems with movement, memory, and balance.

immune effector cell (IEC)-associated polyradiculoneuritis
A possible side effect of anti-BCMA CAR T-cell therapy during which certain nerves become inflamed.

immunoglobulin (Ig)
A protein made by immune system that recognizes threats to the body.

interleukin (IL)
A type of cytokine (small protein) that immune cells use to communicate with each other and coordinate a response to threats in the body.

intravenous immunoglobulin (IVIg)
A solution made from antibodies taken from the blood of healthy donors is given through a vein. Sometimes given to prevent infections after CAR T-cell therapy.

lymphocyte engager therapy
A type of immunotherapy that works by connecting lymphocytes with cancer cells. When they connect—or engage—they make it easier for the immune system to find and kill cancer.

nervous system
Includes the brain, spinal cord, and nerves. It controls everything the body does, including movement, sensation, and breathing.

neurotoxicity
Damage to the nervous system.

seizure
Sudden, uncontrolled body movements and changes in behavior caused by abnormal electrical activity in the brain.

steroids
Inflammation-reducing medicines. They reduce the activity of the immune system. Used to treat side effects of CAR T-cell therapy.

tumor lysis syndrome
A problem caused by treatment of large or fast-growing cancers. The contents of dead cancer cells are released into the blood. This causes problems and may cause organ damage.

vasopressor
Medicine that raises blood pressure by contracting (tightening) blood vessels. Used in emergency situations.



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

NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Management of CAR T-cell and Lymphocyte Engager Related-Toxicities, Version 2.2026. It was adapted, reviewed, and published with help from the following people:

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Fox Chase Cancer Center
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