



NCCN  
GUIDELINES  
FOR PATIENTS®

2025

# Mantle Cell Lymphoma



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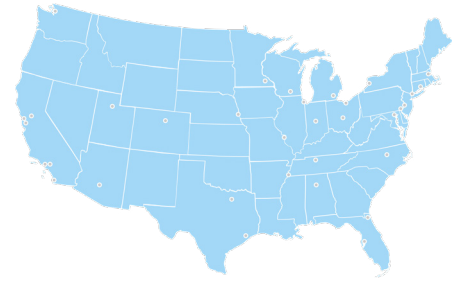
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## About the NCCN Guidelines for Patients®



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®).



Cancer care is always changing. NCCN develops evidence-based cancer care recommendations used by health care providers worldwide. These frequently updated recommendations are the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). The NCCN Guidelines for Patients plainly explain these expert recommendations for people with cancer and caregivers.

**These NCCN Guidelines for Patients are based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas, Version 2.2025 — February 10, 2025.**

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# 1

## About MCL

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**Mantle cell lymphoma is a rare but treatable cancer that affects part of the body's immune system. It's often a fast-growing cancer, but new treatments are giving people more hope and more years to live.**

## What is mantle cell lymphoma?

Mantle cell lymphoma (MCL) is a rare but treatable cancer that develops from certain white blood cells called lymphocytes. Lymphocytes normally protect the body from infection.

Cancer occurs when these cells multiply and grow out of control. An abnormal growth of lymphocytes is a form of cancer called a lymphoma. A lymphoma usually affects the lymphatic system but it can also affect other parts of the body.

## What is the lymphatic system?

The lymphatic system is part of the immune (infection-fighting) system. It transports fluids to the bloodstream and fights germs.

The lymphatic system is made up of lymph fluid, lymph nodes, and other organs. Lymph fluid contains infection-fighting lymphocytes.

Lymph nodes (sometimes called “glands”) are small, bean-shaped structures. Hundreds of lymph nodes are connected by lymph vessels throughout your body.

## Why you should read this book

Making decisions about lymphoma care can be stressful. You may need to make tough decisions under pressure about complex choices.

The NCCN Guidelines for Patients are trusted by patients and providers. They clearly explain current care recommendations made by respected experts in the field. Recommendations are based on the latest research and practices at leading cancer centers.

Cancer care is not the same for everyone. By following expert recommendations for your situation, you are more likely to improve your care and have better outcomes as a result. Use this book as your guide to find the information you need to make important decisions.

As lymph fluid travels through the body, lymph nodes catch and filter out foreign particles and harmful cells. Lymph nodes are usually clustered in groups in your neck, chest, armpits, groin, pelvis, and along your gut. The spleen, tonsils, and thymus are also part of the lymphatic system.

When you get an infection, an army of lymphocytes fills up your lymph nodes to fight it. That's why the lymph nodes in your neck feel swollen when you have a cold, flu, or sinus infection.

## What is a mantle cell?

A mantle cell is a type of B cell inside lymph nodes.

Inside each lymph node are little round clumps of cells called follicles, which play a key role in the immune system.

Follicles contain mostly B cells, a type of lymphocyte that fights bacteria, viruses, and other pathogens. When a foreign substance enters the lymph node, these cells spring into action to break up the substance and get rid of it.

As part of this process, many follicle cells group together into a ball called the germinal center. Inside the germinal center, the cells attack the foreign substance.

Other follicle cells form a circle around the germinal center. This outer area is called the mantle zone. Mantle cell lymphoma starts in B cells in this region inside the lymph node.

## What causes mantle cell lymphoma?

MCL occurs when lymphocytes develop a genetic change that causes them to start overproducing a protein called cyclin D1. This protein stimulates these altered cells to grow out of control and become lymphoma cells.

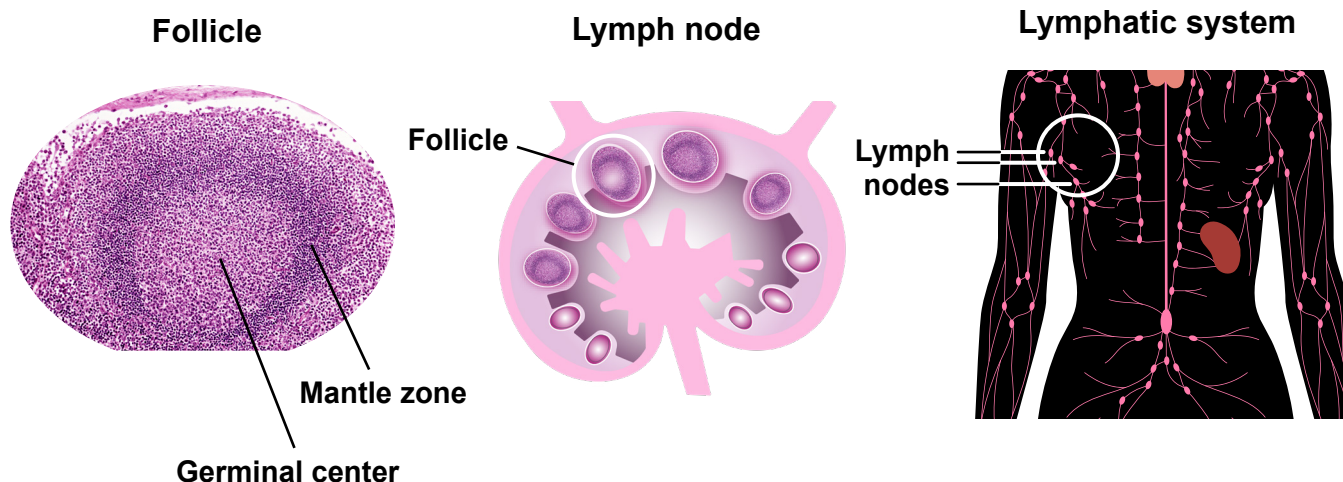
No one knows exactly what causes the mantle zone cells to develop this genetic change, but researchers are working on it.

MCL usually grows quickly over weeks to months. Fast-growing cancers are described as aggressive. However, for some people, MCL grows slowly. Cancer that grows slowly is referred to as indolent.

People who have fast-growing MCL receive different treatment than people with slow-growing MCL.

### Where is the mantle zone?

The mantle zone is a ring of cells that surrounds the germinal center of a follicle (below left), which is a clump of cells inside a lymph node (center) where, normally, disease-fighting cells in the lymphatic system (below right) attack harmful invaders.



## How is mantle cell lymphoma identified?

Mantle cell lymphoma is often discovered when a person has painless, swollen lymph nodes in the neck, armpit, or groin. The lymph nodes swell up because of the overgrowth of lymphoma cells.

Other symptoms may include fever, drenching sweats at night, unexpected weight loss, fatigue, and stomach upset or pain.

Besides the lymph nodes, MCL is commonly found in the spleen, liver, bone marrow, blood stream, and gastrointestinal (GI) tract. The GI tract is made up of the stomach, intestines, and other organs that help digest food.

MCL is usually found in multiple parts of the body when it's first diagnosed. This is referred to as advanced disease. In rare cases, MCL may be limited to a smaller area. This is referred to as localized disease. Advanced disease and localized disease are treated differently.

Multiple tests—like blood tests, genetic tests, and imaging scans—are needed to make sure it's MCL and not another disease or other type of cancer. These tests also find out how widespread the lymphoma is in the body.

Because MCL is a less common form of lymphoma, it can sometimes be difficult to diagnose and treat. If possible, seek out a medical center that specializes in lymphomas. You can also ask for a second opinion.

## How is mantle cell lymphoma treated?

Treatment for MCL can include chemotherapy, immunotherapy, targeted therapy, radiation therapy, cellular therapy, or a combination of these treatments.

MCL is usually a lifelong disease. But treatment can slow down its growth, reduce its symptoms, and prolong your life. For many people, treatment can put MCL into remission. Remission means there are no symptoms or signs of cancer. Remission may last for months or years. However, MCL may come back and need more or stronger treatment.

## What can you do to get the best care?

Advocate for yourself. You have an important role to play in your care. In fact, you're more likely to get the care you want by asking questions and making shared decisions with your care team.

The NCCN Guidelines for Patients will help you understand cancer care. With better understanding, you'll be more prepared to discuss your care with your team and share your concerns. Many people feel more satisfied when they play an active role in their care.

You may not know what to ask your care team. That's common. Each chapter in this book ends with an important section called *Questions to ask*. These suggested questions will help you get more information on all aspects of your care.

Take the next step and keep reading to learn what is the best care for you.

# 2

## Testing for MCL

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**A variety of tests are needed to find out if you have mantle cell lymphoma and to determine how far the lymphoma has grown. Tests are used to plan treatment and to check how well treatment is working.**

If you haven't already been diagnosed, this chapter will help you know what tests you may have and what to expect during testing. The exams and tests used to diagnose MCL are listed on the next page in **Guide 1**.

Bring someone with you to listen when you get test results, ask questions, and write down the answers.

## Health history

Your health care team needs to have all of your health information. They'll ask you about any health issues and treatments you've had.

### Medical history

You'll be asked about any health challenges and treatments you've had during your lifetime. Be ready to talk about:

- Illnesses
- Injuries
- Health conditions
- Symptoms
- Medications and supplements

## Diagnosis vs. Prognosis

What's the difference between your diagnosis and your prognosis? These two words sound alike but they're very different.

**Diagnosis:** The identification of an illness based on tests. The diagnosis names what illness you have.

**Prognosis:** The likely course and outcome of a disease. The prognosis predicts how your disease will turn out.

Mantle cell lymphoma (MCL) can sometimes cause "B symptoms." Let your care team know if you have any of these B symptoms:

- Fevers
- Heavy sweating at night
- Unexplained weight loss

MCL may also affect your gastrointestinal (GI) tract and bone marrow. The GI tract includes the mouth, stomach, intestines, and other organs involved in digestion. GI symptoms that may occur include diarrhea, bloody stools, and pain in your abdomen.

### Family history

You'll also be asked about the health of relatives on both sides of your family. Be prepared to discuss any cancers or other health conditions in your close family members, especially your brothers and sisters, parents, and grandparents.

## Physical exam

A physical exam of your body is done to look for signs of disease. It's also used to help assess what treatments may be options for you.

### Checking for swelling

Certain parts of your body should be checked for swelling. Swelling of lymph nodes (lymphadenopathy) is often the first sign of MCL. Lymph nodes may be so swollen that they can be easily felt or seen under the skin. Your doctor will gently press on the areas of

your body that have lymph nodes, such as your neck, armpits, and groin. Your doctor will also feel your spleen and liver to assess their size.

### Your ability level

Your health care team will also rate your overall health and ability to do basic daily activities like walking, cleaning, bathing, and so forth.

This is known as performance status. Doctors do this for several reasons, one of which is to learn whether you can handle intense therapy.

#### Guide 1

#### Health exams and tests before lymphoma treatment

<b>Health history and exams</b>	<ul style="list-style-type: none"> <li>• Medical history, including B symptoms</li> <li>• Physical exam, including lymph nodes, liver, and spleen</li> <li>• Ability to do daily activities (performance status)</li> </ul>
<b>Blood tests</b>	<ul style="list-style-type: none"> <li>• Complete blood count (CBC) with differential</li> <li>• Comprehensive metabolic panel</li> <li>• Lactate dehydrogenase (LDH)</li> <li>• Uric acid</li> <li>• Beta-2 microglobulin</li> </ul>
<b>Infectious disease tests</b>	<ul style="list-style-type: none"> <li>• Hepatitis B test</li> <li>• Hepatitis C test</li> </ul>
<b>Imaging</b>	<ul style="list-style-type: none"> <li>• CT or PET/CT scans of chest, abdomen, pelvis (and neck, if needed) with contrast</li> </ul>
<b>Heart tests</b>	<ul style="list-style-type: none"> <li>• Echocardiogram or MUGA scan, if certain chemotherapy is planned</li> </ul>
<b>Biopsies</b>	<ul style="list-style-type: none"> <li>• Lymph node biopsy</li> <li>• Bone marrow aspiration and biopsy, if needed</li> <li>• Endoscopy or colonoscopy, if needed</li> <li>• Lumbar puncture, if needed</li> </ul>

## Blood tests

MCL can cause abnormal blood counts. Doctors test blood to look for this and other signs of disease. Blood tests are also used to learn when treatment should begin.

A blood test requires a sample of your blood. The sample is removed with a needle inserted into a vein. This is called a blood draw.

Tests that may be done with your blood sample include:

### **CBC with differential**

A complete blood count (CBC) measures parts of the blood. Test results include measurements of white blood cells, red blood cells, and platelets. Lymphoma and other health conditions can cause low or high counts.

There are five types of white blood cells. A differential counts the number of each type of white blood cell. It also checks if the cell counts are in balance with each other.

### **Comprehensive metabolic panel**

Your liver, bone, and other organs release chemicals into your blood. A comprehensive metabolic panel includes tests for up to 14 of these chemicals. The tests show if the levels of chemicals are too low or high. Abnormal levels can be caused by lymphoma or other health conditions.

### **LDH**

High levels of the protein lactate dehydrogenase (LDH) can be caused by lymphoma or other health problems. If related to lymphoma, high levels of LDH may be a sign that treatment may be needed soon.

### **Beta-2 microglobulin**

High levels of beta-2 microglobulin can be caused by lymphoma as well as other health conditions, like kidney disease.

### **Swollen glands**

**Swelling of lymph nodes (such as the “glands” in your throat) is often one of the first signs of mantle cell lymphoma. Lymph nodes may be so swollen that they can be easily felt or seen under the skin. Your doctor will gently press on the areas of your body that have lymph nodes, such as your neck, armpits, and groin.**



### Uric acid

Uric acid is released by cells when DNA breaks down. You may have a high level of uric acid before starting treatment. Levels can be high due to fast-growing lymphoma, kidney disease, or other health conditions.

### Hepatitis tests

Some types of lymphoma treatments can weaken your immune system. This increases your chance of getting infections. Hepatitis B and hepatitis C infections in particular can become active again from certain therapies. So, it's important to be tested for hepatitis viruses.

## Biopsies

The only way to be sure that you have lymphoma is to test fluid or tissue for lymphoma cells. A biopsy is a procedure that removes a sample of fluid or tissue for testing. There are several types of biopsies.

### Lymph node biopsy

For B-cell lymphomas like MCL, experts from NCCN advise getting an incisional or excisional biopsy of the lymph node(s). These biopsies remove lymph node tissue through a cut into your skin.

In certain situations, a core needle biopsy may be necessary if the lymph node is difficult to get to. For a core needle biopsy, your clinician (usually an interventional radiologist) uses CT or ultrasound imaging to guide a long, hollow needle to obtain a sample of the lymph node tissue.

### Bone marrow aspiration and biopsy

MCL can develop in bone marrow, which is part of the lymphatic system. A bone marrow biopsy removes a core of bone and soft bone marrow. A bone marrow aspiration removes liquid bone marrow. Both procedures may be done at the same time. The samples will be sent to a lab for lymphoma testing.

### Biopsy

**A lymph node biopsy is a minor surgical procedure to remove a part or a whole lymph node. In this photo, the health care provider is using an ultrasound monitor to locate the area in the body to be biopsied. After the procedure, the biopsy sample is tested to find out if it has lymphoma cells.**



### GI biopsy

Compared with other types of lymphoma, MCL is more likely to involve the GI tract. To see inside the GI tract, doctors use procedures called endoscopy and colonoscopy. A device called an endoscope is used in the upper GI tract. A device called a colonoscope is used in the lower GI tract. Samples of tissue that may have lymphoma will be removed and tested.

### Lumbar puncture

A lumbar puncture is a procedure that removes a sample of spinal fluid. It's also called a spinal tap. Your doctor may suspect that the lymphoma is in spinal fluid based on symptoms or the lymphoma type.

## Imaging

Imaging makes pictures of the insides of your body. It's used to detect lymphoma in deep lymph nodes, organs, bone marrow, and other parts of the body. It provides useful information

to determine the extent of lymphoma involvement.

### PET/CT

Positron emission tomography (PET) and computed tomography (CT or CAT scan) are two types of imaging. When used together, they're called a PET/CT scan. The PET/CT scan is used to image your whole body.

These tests often are used together to get the best picture before and after treatment.

### PET scan

A PET scan requires injecting a substance called a radiotracer into your bloodstream. The radiotracer is detected with a special camera during the scan. It highlights cells that may be lymphoma. Afterward, the tracer leaves your body in your urine.

### CT scan

A CT scan identifies lymph nodes and other tissues that may be enlarged. It uses x-rays to take many images from different angles. A computer then combines the pictures to

### PET/CT scan

This is a PET/CT scanner. Imaging instruments, like this one, can detect even small amounts of lymphoma in your body.

During the scan, you lie down on a table that moves into the tunnel of the machine.



make a series of cross-sectional images of your body. A CT scan of your chest, belly area, and between your hip bones is needed to help diagnose MCL. You may also need a CT of your neck to look for lymphoma in lymph nodes.

Sometimes a contrast agent (also called contrast dye) is used to make the pictures clearer. Contrast is injected into the bloodstream and flushed out in urine.

### Diagnostic tests

Cancers of blood cells, like MCL, can be difficult to tell apart. Diagnostic tests reveal which lymphoma you have.

For these tests, your blood and tissue samples are sent to a laboratory. At the lab, a doctor called a hematopathologist tests the samples to look for signs (markers) of MCL. Hematopathologists are experts at diagnosing lymphomas in blood cells.

Two tests they use are protein tests and molecular tests.

### Protein tests

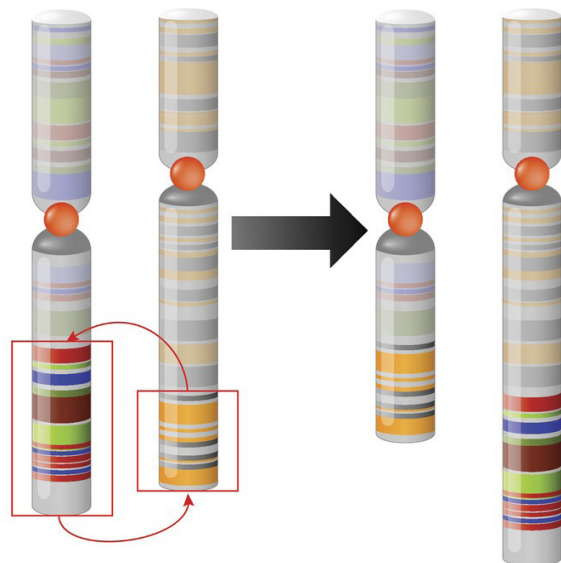
The hematopathologist will test your samples to look for proteins on the surface and inside of lymphoma cells. The hematopathologist looks for common patterns of proteins in the sample. Finding, or not finding, these proteins can reveal the type of lymphoma.

For example, MCL cells have high levels of a protein called cyclin D1, as well as CD5, CD20, and other specific proteins. At the same time, the proteins CD200 and LEF1 are usually missing in MCL. So a sample that contains the first group of proteins but doesn't contain the second two proteins suggests a diagnosis of MCL.

Similarly, most people with typical MCL have lymphoma cells that produce the SOX11 protein. On the other hand, having a low or absent level of the SOX11 protein may indicate slow-growing MCL.

### Translocation

**A translocation means that parts of two chromosomes are switched. The translocation in mantle cell lymphoma occurs when the bottom of chromosome 11 switches places with the bottom of chromosome 14. This leads to an increase in cyclin D1, a protein that helps control the cell cycle. The presence of too much cyclin D1 is one of the key features of MCL.**



Ki-67 is another protein that's important in MCL. High levels of Ki-67 are linked to a type of MCL that grows quickly.

The hematopathologist will also look at your cells under a microscope to find any visible abnormalities. For instance, large, rapidly-dividing cells may indicate a rare subtype of MCL called blastoid variant. This MCL subtype may be seen at diagnosis or appear later on. The blastoid variant grows faster and is more difficult to treat than typical MCL.

### Molecular biomarker tests

Genes and chromosomes contain the instructions to make cells work and to make new cells. Abnormal changes in genes and chromosomes can lead to lymphoma. Sometimes it helps to test for these changes. The results can be used for diagnosis and prognosis.

Most MCL cells are known to have a specific change, called a translocation, in their chromosomes. A translocation means that parts are switched between two chromosomes.

The MCL translocation occurs when a part of chromosome 14 trades places with a part of chromosome 11. This translocation is what causes cells to make too much cyclin D1, a protein that helps control the cell cycle. Too much of this protein leads to the development of MCL. Using biopsy samples, the hematopathologist can test the chromosomes in your cells to find out if they have this genetic abnormality.

Other changes are also involved in MCL. Certain abnormal changes in genes can affect how well the lymphoma is likely to respond to treatment. So it may be useful to test for certain genes that have abnormal changes.



### What is high-risk MCL?

People who have an abnormal change in the *TP53* gene have a high-risk type of mantle cell lymphoma.

Having this genetic mutation means the lymphoma is likely to be fast growing. Standard lymphoma treatments don't work as well against this type of MCL, so there's a greater likelihood for poor results.

Experts strongly recommend that people with this type of high-risk MCL try to enroll in a clinical trial.

In particular, an abnormal change in the *TP53* gene is linked to faster-growing MCL and poor results with standard lymphoma treatment. So it's important to check for this *TP53* mutation and other potential changes that could affect your treatment.

### Heart tests

Some lymphoma treatments can damage your heart. To plan treatment, your doctor may test how well your heart pumps blood.

You may get an echocardiogram or multigated acquisition (MUGA) scan. An echocardiogram uses sound waves to make pictures of your heart. A MUGA scan makes pictures using a tracer and special camera.

## Fertility and pregnancy

Some lymphoma treatments may affect your ability to conceive or bear children. However, options are available. Sperm can be frozen and stored in a sperm bank until after lymphoma treatment. Eggs can be removed from ovaries and stored for later use. Discuss your thoughts and preferences with your health care team.

Some lymphoma treatments can harm an unborn baby. If you might be pregnant now, expect your health care team to order a pregnancy test before you start treatment. Also, take steps to avoid getting pregnant or causing a pregnancy during treatment. Your care team can tell you which birth control methods are best to use.



**Report any unusual feelings of sadness, loss of interest in activities, anxiety, and sleep problems to your doctor. Many people experience these feelings, and they should not go untreated.”**

### Tips for testing

Results from blood tests, imaging studies, and biopsies will be used to determine your treatment plan. It's important you understand what these tests mean. Ask questions and keep copies of your test results. Online patient portals are a handy way to access your test results.

Follow these tips for testing:

- **Bring someone with you** to doctor visits, if possible. They can ask questions and remember what was said.
- **Get copies** of your test results including blood tests, imaging scans, and lab reports.
- **Write down questions** and take notes during appointments. Don't be afraid to ask your care team questions. You can ask if it's okay to record your talks.
- **Organize your papers.** Create files for insurance forms, medical records, and test results. You can do the same on your computer.
- **Keep a list of contact information** for everyone on your care team. Add it to your phone. Hang the list on your refrigerator or keep it in a place where someone can access it in an emergency. Keep your primary care clinician informed of any changes.

## Key points

- › Your health care team will check the size of your lymph nodes, spleen, and liver.
- › Blood tests will be done to look for signs of lymphoma and other health issues.
- › A lymph node biopsy is the only way to be sure that you have mantle cell lymphoma. Other areas of your body may also need to be biopsied.
- › Imaging tests allow your care providers to look inside your body to find where the lymphoma is located.
- › Protein tests identify a signature-like pattern of proteins that can reveal whether you have MCL or another type of lymphoma.
- › Molecular tests can find certain genetic changes that may confirm the diagnosis and help understand your prognosis.



**Try to remember that everyone's journey is different. Your physiological, mental, emotional, and spiritual response is unique."**

## Questions to ask

- › Where do I go to get tested? How long will the tests take? Will any test hurt?
- › Will my insurance pay for all of the tests you're recommending?
- › How soon will I know the results and who will explain them to me?
- › Who will talk with me about the next steps? When?
- › Is my lymphoma fast-growing or slow-growing? How far has it spread?

# 3

## Types of treatment for MCL

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**There isn't one single recommended treatment for MCL—there are many treatment options. You and your health care team will work together to figure out the best treatment for you.**

Treatment decisions are based on different factors such as your age, level of fitness (performance status), and overall health. Often the most important factor is the extent of the lymphoma. Doctors classify this by cancer stage.

## Cancer stage

A cancer stage is a number that stands for the extent of cancer in the body. For mantle cell lymphoma (MCL), the extent of lymphoma depends on its locations. A lower number means fewer areas of lymphoma development in the body and a higher number means more. This number is based mostly on the results from your biopsies, blood tests, and imaging.

Doctors use a specific rating system for most lymphomas. This system includes four stages. For treatment purposes, the stages are often grouped together like this:

**Stage 1 and stage 2** refer to the early stages of MCL. These lymphomas haven't progressed to many locations in the body. MCL is rarely diagnosed at these stages. For more information about stage 1 and stage 2 mantle cell lymphomas, see Chapter 5.

**Stage 3 and stage 4** are advanced stages of MCL. In these stages, the lymphoma occurs

in lymph nodes in several areas in the body. It may also be found in the spleen, bone marrow, or other organs. Almost all people with MCL are diagnosed when the lymphoma has reached these stages.

Treatment options for advanced MCL are partly based on how fast the lymphoma is growing. Advanced MCL is described as fast growing or slow growing. Most people who are diagnosed with advanced MCL have the fast-growing kind.

## Treatment types

Treating MCL includes treatment of the lymphoma and support for you.

The aim of treatment is to reduce symptoms, control the cancer, get the lymphoma into remission, and extend life. Remission means that the lymphoma can't be detected.

Researchers are always testing new treatments. Newer treatments are helping people with MCL live longer with fewer health challenges than before. While MCL can be thought of as an ongoing (chronic) disease, many people are now achieving complete remission.

Not everyone receives the same treatment. Also, some people can handle more intense treatment while others cannot. Your doctor will tailor your treatment based on the tests described in *Chapter 2: Testing for MCL*.

## Why some therapies are preferred

NCCN experts recommend treatments based on science evidence and safety. Their recommendations are grouped into 3 categories:

**Preferred therapies** have the most evidence they work better and may be safer than other therapies.

**Other recommended therapies** may not work quite as well as preferred therapies, but they can still help treat lymphoma.

**Therapies used in certain cases** work best for people with specific lymphoma features or health circumstances.

Current types of treatment for MCL include:

#### **Chemoimmunotherapy**

This treatment combines the use of chemotherapy and immunotherapy. These treatments used together are often more effective than both treatments used separately.

**Chemotherapy** uses drugs to damage and destroy rapidly dividing cells, like lymphoma cells. Chemotherapy harms healthy cells, too. That's why it can cause side effects. Some

chemotherapy drugs are given through an intravenous (IV) infusion into a vein in your arm or another part of your body. Other types of chemotherapy can be taken as a pill.

Chemotherapy is given in treatment cycles. One cycle is made up of a few treatment days followed by a period of rest. This lets the body recover before the next cycle. One cycle is often 3 or 4 weeks long. However, the cycle schedule varies depending on which drugs are used.

**Immunotherapy** consists of medicines that are based on antibodies. Antibodies are natural proteins of the immune system. They help your body fight germs and other threats.

Antibodies can also be made in a lab. These antibodies are designed to treat specific types of lymphoma. Rituximab (Rituxan) is a monoclonal antibody treatment for MCL. It recognizes and attaches to a specific protein (CD20) that's found on the surface of most B

#### **Chemoimmunotherapy**

**Chemoimmunotherapy combines chemotherapy and immunotherapy treatments. These treatments used together are often more effective than both treatments used separately.**

**Some chemotherapy drugs are given through an intravenous (IV) infusion into a vein in your arm. This patient is receiving chemotherapy through an IV access port in the upper chest.**



cells. Rituximab marks these cells so that your immune system can find and destroy them. Rituximab is given through an IV.

For chemoimmunotherapy, some regimens are intense and some are less intense. Good results can be achieved with both types of regimens. Intense regimens have more risk of side effects, so they aren't often given to older adults or those with other health conditions.

### Targeted therapy

Targeted therapy drugs attack certain molecules in lymphoma cells to halt their growth and spread. Targeted therapy harms normal cells less than chemotherapy does.

Types of targeted therapies for MCL include:

- **Kinase inhibitors** – Kinases are enzymes with many cell functions. A kinase called Bruton's tyrosine kinase (BTK) helps cancerous B cells develop and grow. Drugs that block BTK can reduce the number of new MCL cells that are made. These drugs, called BTK inhibitors, include acalabrutinib (Calquence), ibrutinib (Imbruvica), pirtobrutinib (Jaypirca), and zanubrutinib (Brukinsa). BTK inhibitors are oral medicines given as capsules or tablets.
- **BCL-2 inhibitors** – BCL-2 is a protein inside of B cells that helps prevent cell death. BCL-2 can build up in lymphoma cells and save them from dying. Venetoclax (Venclexta) is a drug that blocks the effect of BCL-2. This allows the lymphoma cells to self-destruct. Venetoclax is given as a pill. It's currently in clinical trials for treating MCL.



### What is a regimen?

A regimen is a plan that defines the dosage, schedule, and duration of a treatment. Regimens for MCL often include multiple drugs.

- **Proteasome inhibitors** – Bortezomib (Velcade) is a drug that targets proteasomes inside lymphoma cells. Proteasomes are sometimes called the cell's "garbage disposal" because they grind up and get rid of the cell's waste. Bortezomib halts the proteasomes from working. This causes a pile-up of waste within the lymphoma cell, which can poison and kill it. Bortezomib is given through an IV into a vein or under the skin.
- **Bispecific antibody** – A bispecific antibody is a drug that targets two different types of cells at the same time. Glofitamab-gxbm (Columvi) is a bispecific antibody that attaches to B cells, which can become cancerous, and to T cells, which are immune cells that fight cancer cells. When the drug binds to one of each cell, the T cell attacks and destroys the B cell. Glofitamab-gxbm can only be used to treat certain cases of relapsed or refractory MCL.

### Immunomodulators

Immunomodulators are drugs that are used in lymphoma care to boost the immune system. Lenalidomide (Revlimid) is an immunomodulator that's used to treat MCL. It's given as a capsule. Other drugs, like rituximab and ibrutinib, may be used with lenalidomide.

### Active surveillance

In some cases, no treatment is the right treatment. For MCL, this may be the case with slow-growing MCL that isn't causing any symptoms. While treatment may not be necessary, having regular tests and visits is recommended to see if the lymphoma begins to grow. This is why it's called active surveillance. (It's also called watch-and-wait.) If symptoms begin, treatment will also begin.

### Radiation therapy

Radiation therapy uses high-energy x-rays to treat MCL. The x-rays damage the DNA in lymphoma cells. This either kills the lymphoma cells or stops new lymphoma cells from being made.

A very focused type of radiation, involved-site radiation therapy (ISRT), is used for MCL that's confined to a limited area. ISRT targets only the lymphoma in the lymph node or affected area while avoiding the surrounding areas. This reduces many of the side effects of regular radiation therapy.

Radiation therapy may also be used for MCL that comes back after treatment (relapse).

### Stem cell transplant

A stem cell transplant replaces unhealthy, damaged, or destroyed stem cells with healthy stem cells. The healthy stem cells form new bone marrow and new blood cells.

A stem cell transplant is an intense treatment. It's now used only in certain cases for treating MCL. So it may not be part of your care plan.

There are 2 types of stem cell transplants:

- **An autologous transplant** is also called high-dose therapy with autologous stem cell rescue (or HDT/ASCR). First, many of your healthy stem cells will be removed and stored for later. Next, you'll receive high doses of chemotherapy to destroy the lymphoma cells. Chemotherapy will also wipe out the blood-producing cells in the bone marrow. Your healthy stem cells will then be returned to your body to "rescue" your bone marrow.
- **An allogeneic transplant** uses healthy stem cells from a donor. You'll first receive treatment, called conditioning, to eliminate as much lymphoma as possible and help prevent your body from rejecting the transplanted cells. Next, you'll receive the donor cells, which will form new, healthy bone marrow and a new immune system. The new immune system will then attack lymphoma cells that weren't killed by earlier treatment.

### CAR T-cell therapy

This treatment may be used if chemoimmunotherapy and targeted therapy aren't enough to halt the lymphoma. Chimeric antigen receptor (CAR) T-cell therapy is a treatment made from your own T cells. T

cells are lymphocytes that hunt and destroy lymphoma cells, infected cells, and other damaged cells. However, lymphoma cells learn how to hide from your T cells, which allows the lymphoma to grow. CAR T-cell therapy reprograms your natural T cells to recognize and attack lymphoma cells.

First, your own T cells are removed from your body using a special machine. At a lab, the gene for a chimeric antigen receptor (CAR) is added to your T cells. This genetically alters the T cells to hunt specifically for lymphoma cells. The CAR T cells are infused back into your body where they find and kill MCL cells.

## Clinical trials

Therapy may also be given as part of a clinical trial. A clinical trial is a type of medical research study. After being developed and tested in a lab, potential new ways of fighting cancer need to be studied in people.

If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. Food and Drug Administration (FDA).

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for you.

## Phases

Most cancer clinical trials focus on treatment and are done in phases.

- **Phase 1** trials study the safety and side effects of an investigational drug or treatment approach.



## Finding a clinical trial

### In the United States

#### NCCN Cancer Centers

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

#### The National Cancer Institute (NCI)

[cancer.gov/about-cancer/treatment/clinical-trials/search](https://www.cancer.gov/about-cancer/treatment/clinical-trials/search)

### Worldwide

#### The U.S. National Library of Medicine (NLM)

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

## Need help finding a clinical trial?

#### NCI's Cancer Information Service (CIS)

1.800.4.CANCER (1.800.422.6237)

[cancer.gov/contact](https://www.cancer.gov/contact)

- **Phase 2** trials study how well the drug or approach works against a specific type of cancer.
- **Phase 3** trials test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.

- ▶ **Phase 4** trials study the safety and benefit of an FDA-approved treatment.

#### Who can enroll?

It depends on the clinical trial's rules, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. They ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

#### Informed consent

Clinical trials are managed by a research team. This group of experts will review the study with you in detail, including its purpose and the risks and benefits of joining.

All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss it with people you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

#### Will I get a placebo?

Placebos (inactive versions of real medicines) are never used alone in clinical trials. It is common to receive either a placebo with a standard treatment, or a new drug with a standard treatment.

You will be informed, verbally and in writing, if a placebo is part of a clinical trial before you enroll.

#### Are clinical trials free?

There is no fee to enroll in a clinical trial. The study sponsor pays for research-related costs, including the study drug. But you may need to pay for other services, like transportation or childcare, due to extra appointments.

During the trial, you will continue to receive standard lymphoma care. This care is often covered by insurance.

**“Ask your oncologist for a list of possible side effects right before each treatment. Track your side effects and report them to your doctor.”**



## Treatment for side effects

All treatments can cause unwanted health problems called side effects. Some side effects may be harmful to your health. Others may just be unpleasant.

Different treatments have different side effects. Side effects also depend on the length or dose of treatment and the person.

Most side effects appear shortly after treatment starts and go away in days or weeks after treatment is over. Other side effects may be long term or appear years later.

Don't ignore or disregard side effects. If left untreated, side effects may delay your scheduled treatment. Tell your health care team about any new or worse symptoms you have.

Ask your treatment team for a complete list of the side effects of your treatments. There are ways to prevent some side effects and help you feel better.

## Supportive care

Supportive care helps improve your quality of life during and after lymphoma treatment. The goal is to prevent or manage side effects and symptoms, like pain and fatigue.

Supportive care also addresses the mental, social, and spiritual concerns faced by those with MCL.

Supportive care (also called palliative care) is available to everyone with MCL and their families, not just those at the end of life.

In fact, people who start supportive care when they begin treatment tend to have improved outcomes and better quality of life.

### Common side effects of MCL treatments

- tiredness
- nausea
- vomiting
- diarrhea
- headache
- low blood cell counts
- constipation
- infection
- fever or chills
- decreased appetite
- rash
- sores and swelling in the mouth
- shortness of breath
- irregular heartbeat
- hair loss
- tingling, numbness, or pain in hands or feet

Supportive care can also help with:

- Making treatment decisions
- Coordinating your care
- Finding ways to pay for care
- Planning for advanced care and end of life

Read more about supportive care in *Chapter 6: Treatment for recurrent MCL*.

## Key points

- Often the most important factor for deciding treatment is the extent of the lymphoma—how much it has grown.
- Stage 1 and stage 2 refer to the early stages of MCL. MCL is rarely diagnosed at these stages.
- Stage 3 and stage 4 are advanced or later stages of MCL. Almost all people with MCL are diagnosed when the lymphoma has reached these stages.
- Chemotherapy uses drugs to kill lymphoma cells. Immunotherapy uses manufactured antibodies to destroy lymphoma cells. Chemoimmunotherapy is a more effective combination of these two treatments.
- Targeted therapy drugs attack certain lymphoma cells to slow their growth.
- Clinical trials give people access to new tests and treatments that they couldn't usually receive otherwise.
- All treatments cause side effects. Be sure to tell your treatment team if you get any physical or emotional effects after treatment.



**A common myth is that palliative care is only for terminally ill patients. It is so much more! Palliative care providers treat the whole patient, not just cancer. It's worth reaching out to palliative care in your hospital or clinic.”**

## Questions to ask

- What are my treatment options?
- What are the benefits and risks of each treatment option?
- Are you suggesting treatment options from the NCCN Guidelines, or have you modified the standard approach in my situation?
- Will the treatment hurt or cause a lot of side effects?
- How do I get a second opinion?

# 4

## Treatment for advanced MCL

28 Treatment for fast-growing MCL

32 Treatment for slow-growing MCL

33 Key points

33 Questions to ask

**Most people diagnosed with mantle cell lymphoma (MCL) have advanced disease. Advanced MCL requires intense therapy, but treatment methods continue to evolve. This chapter explains the treatment process.**

People who have stage 3 or stage 4 mantle cell lymphoma (MCL) are considered to have advanced MCL. (For information about early-stage MCL, see *Chapter 5: Treatment for early MCL*.)

The goal of treating advanced MCL is to remove as much lymphoma as possible and keep the disease under control. Treatment may continue for months or even years.

Treatment for advanced MCL depends on whether the lymphoma is growing fast or growing slow.

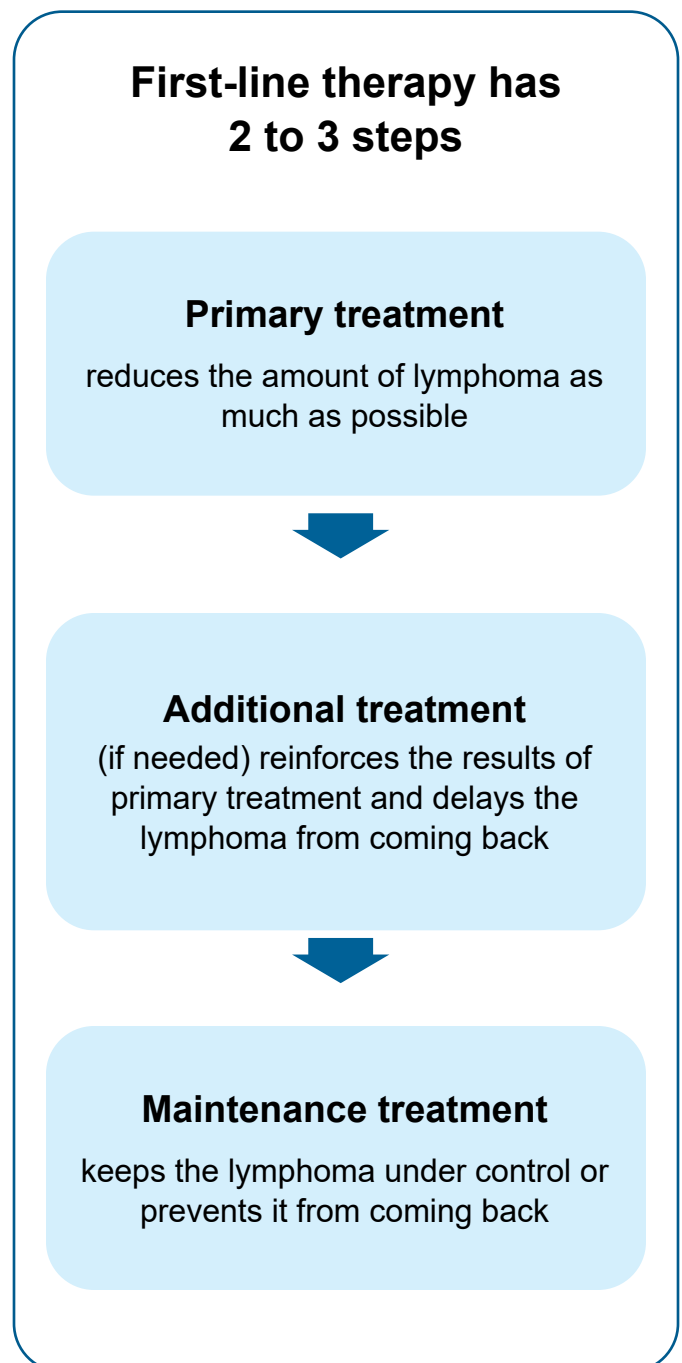
Most people who are diagnosed with advanced MCL have the fast-growing type. For treatment for the fast-growing type, read the next section. (For treatment for slow-growing MCL, see page 32.)

## Treatment for fast-growing MCL

Fast-growing, advanced MCL usually requires more than one type of therapy. The first therapy you're given is called first-line therapy. If the lymphoma comes back after first-line treatment, your treatment team will suggest another therapy (second-line treatment).

If the lymphoma comes back after both the first-line and the second-line treatment, you may want to try a third (third-line) treatment.

Another recommended treatment option for people with advanced MCL is to find an appropriate clinical trial.



## First-line therapy

First-line therapy is given in 3 phases: primary treatment, additional treatment (if needed), and maintenance treatment.

### Primary treatment

The goal of primary treatment is to reduce the amount of lymphoma as much as possible. The choice of treatment depends on whether your body can handle intense (aggressive) therapy. Preferred primary treatments are listed in **Guide 2**.

If your body can't handle aggressive treatment, see the preferred options for moderate treatment in **Guide 3**.

After the primary treatment, your provider will evaluate the results to see how well the therapy worked:

- **Complete response** – If tests can no longer detect the lymphoma, you've had a complete response to primary treatment. A complete response is also called remission. The lymphoma can still return,

## Guide 2

### Aggressive primary treatments for advanced MCL

Preferred treatments	LYMA regimen	<ul style="list-style-type: none"> <li>• RDHAP (rituximab, dexamethasone, cytarabine, and platinum-based chemotherapy) followed by RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)</li> </ul>
	NORDIC regimen	<ul style="list-style-type: none"> <li>• Dose-intensified chemoimmunotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone, alternating with rituximab and high-dose cytarabine</li> </ul>
	BR followed by rituximab and high-dose cytarabine	<ul style="list-style-type: none"> <li>• Bendamustine and rituximab, followed by rituximab and high-dose cytarabine</li> </ul>
	TRIANGLE regimen	<ul style="list-style-type: none"> <li>• RCHOP and ibrutinib, alternating with RDHAP</li> </ul>
Other recommended treatments	HyperCVAD+R	<ul style="list-style-type: none"> <li>• HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine) and rituximab</li> </ul>
	RBAC	<ul style="list-style-type: none"> <li>• Rituximab, bendamustine, and cytarabine</li> </ul>

but you can stop primary treatment and begin maintenance treatment.

- **Partial response** – A partial response to primary treatment means that the lymphoma has decreased in size but is still there. If you have a partial response, you may need additional treatment.
- **No response** – If the lymphoma continues to grow or seems unaffected by first-line therapy, you can have additional lines of therapy. See *Chapter 6: Treatment for recurrent MCL*.

**Additional treatment**

If you have a **complete response** to the primary treatment, then you could have additional treatment to bolster the results of

primary treatment and delay the lymphoma from coming back.

A few years ago, the additional treatment for many people with MCL was high-dose chemotherapy followed by an autologous stem cell transplant (HDT/ASCR), which is an intense procedure.

More recently, researchers have found that newer targeted therapies can be more effective than HDT/ASCR. As a result, HDT/ASCR isn't recommended as often for most people with MCL.

Instead, additional treatment often involves targeted therapy with a BTK inhibitor (acalabrutinib, ibrutinib, or zanubrutinib). Trying to enroll in a clinical trial may also be an option.

**Guide 3**

**Less aggressive primary treatments for advanced MCL**

<b>Preferred treatments</b>	<b>ABR</b>	• Acalabrutinib, bendamustine, and rituximab
	<b>BR</b>	• Bendamustine and rituximab
	<b>VR-CAP</b>	• Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone
	<b>RCHOP</b>	• Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
	<b>LR</b>	• Lenalidomide and rituximab
<b>Other recommended treatment</b>	<b>AR</b>	• Acalabrutinib and rituximab

If you had a **partial response** to primary treatment, you could have additional therapy to try to get the lymphoma into remission. The preferred additional therapy is targeted treatment with a BTK inhibitor (if you haven't been treated with a BTK inhibitor before).

Chemoimmunotherapy is another treatment option that might provide a complete response.

### Maintenance treatment

The goal of maintenance treatment is to prevent or delay the lymphoma from coming back. Or, if MCL is still present, maintenance treatment may keep the lymphoma under control.

Maintenance treatment typically includes rituximab given by intravenous (IV) infusion every 8 weeks for up to 2 to 3 years. If you received aggressive primary treatment, maintenance treatment may also include a BTK inhibitor for 2 years.

### Follow-up care

During the maintenance phase, you'll have follow-up visits with your care team. You'll also be tested for any signs that MCL has returned (relapsed) and be checked for any side effects.

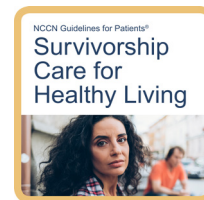
If you have a relapse or recurrence, you can ask your care team to help you find a clinical trial. If you can't find a suitable clinical trial, you can move on to second-line treatment. For information on second-line treatment, see *Chapter 6: Treatment for recurrent MCL*.



## What is a relapse?

Although newer approaches to treatment have improved results, most people with MCL eventually experience a relapse. A relapse is when lymphoma gets better after treatment but later returns.

Unfortunately, most lymphoma drugs begin to lose their effect against the lymphoma sooner or later. The lymphoma becomes "resistant" to the drug. This is the main reason why relapses occur. Each time MCL relapses, it may be more difficult to treat it than the time before.



## Survivorship

Living with cancer is called survivorship. It starts when your lymphoma is diagnosed. Read more about survivorship in *NCCN Guidelines for Patients: Survivorship Care for Healthy Living*, available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](https://www.nccn.org/patientguidelines) app.

## Treatment for slow-growing MCL

People with slow-growing MCL often have no symptoms and no swollen glands when they're diagnosed. The lymphoma exists only in their bone marrow and blood (although some may have it in their spleen or gastrointestinal tract).

For people with slow-growing MCL that has no symptoms, doctors often take a watch-and-wait (active surveillance) approach instead of starting treatment immediately. MCL can grow

slowly for months, or even years, before it needs to be treated.

If MCL symptoms begin, you'll need to be re-evaluated. Your doctor will assess if the lymphoma is now growing faster. It may be biopsied again and tested for a genetic *TP53* mutation. Most people with MCL don't have a *TP53* mutation.

If you develop MCL symptoms or have other signs that the lymphoma is growing, then you and your care team should decide whether treatment should begin. To find out about treatment for fast-growing MCL, see page 28.



### Treatment for MCL with a *TP53* mutation

If molecular biomarker testing found that your lymphoma has a change in the *TP53* gene, NCCN experts strongly recommend participating in a clinical trial as an initial treatment option.

If you don't want to try to enroll in a clinical trial or no clinical trials are available, a new treatment combination may help. It consists of zanubrutinib (Brukinsa), obinutuzumab (Gazyva), and venetoclax (Venclexta).

Otherwise, treatment depends on whether your body can handle aggressive therapy.

**Aggressive therapy** – If you can undergo aggressive therapy, the recommended first treatment is the TRIANGLE regimen, which is described in **Guide 2**. This regimen is followed by maintenance therapy with rituximab infusion every 8 weeks for 3 years as well as daily ibrutinib for 2 years, or until the lymphoma returns.

**Less aggressive therapy** – If your care team recommends less aggressive first-line therapy, see the treatment options in **Guide 3**. Depending on which primary treatment you have, you may receive maintenance therapy with rituximab every 8 weeks for 2 to 3 years, or until the lymphoma returns.

## Key points

- The goal of treatment is to remove as much lymphoma as possible and keep the disease under control.
- First-line treatment is often given in phases. The first phase is primary therapy. The most common primary therapy for advanced MCL is chemoimmunotherapy with or without a BTK inhibitor.
- Primary treatment may be followed by either additional treatment or maintenance treatment, or both.
- Additional treatment often involves targeted treatment with a BTK inhibitor. Maintenance treatment often involves rituximab.
- If first-line treatment doesn't work or the lymphoma relapses, you may receive the same or a different type of treatment (second-line treatment).
- People with slow-growing MCL who have no symptoms usually don't get treatment. But they'll continue to be tested to detect any changes.

## Questions to ask

- What is your experience as well as your team's experience with treating the type of lymphoma I have?
- Are my chances any better for one treatment than another? Less time-consuming? Less expensive?
- How will you know if the treatment is working?
- What are my options if treatment stops working?
- What supportive care services are available to me during and after treatment?

# 5

## Treatment for early MCL

35 Treatment for stage 1 and stage 2 MCL

37 Key points

37 Questions to ask

**Most people with mantle cell lymphoma (MCL) are diagnosed at a more advanced stage. But a small number of people have early-stage MCL. This chapter discusses how early MCL can be treated.**

The early stages of mantle cell lymphoma (MCL) are stage 1 and stage 2.

Stage 1 MCL is defined as lymphoma in one lymph node or in one group of nearby lymph nodes. Stage 2 MCL has affected two or more lymph nodes or groups of nearby lymph nodes.

Because these lymphomas occur in fewer areas in the body, people seldom show significant symptoms. That's one reason why MCL is rarely diagnosed at these stages.

## Treatment for stage 1 and stage 2 MCL

### Initial treatment

Either radiation therapy or chemoimmunotherapy, or both, may be enough to control stage 1 or stage 2 MCL. Chemoimmunotherapy options for early MCL are listed in **Guide 4**.

In some cases, treatment for stage 1 or stage 2 MCL may not be needed right away. Instead, a watch-and-wait approach (also called active surveillance) is used to decide when to start treatment.

### Guide 4 Drug treatment options for early MCL

<b>Preferred treatments</b>	<b>ABR</b>	• Acalabrutinib, bendamustine, and rituximab
	<b>BR</b>	• Bendamustine and rituximab
	<b>VR-CAP</b>	• Bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone
	<b>RCHOP</b>	• Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
	<b>LR</b>	• Lenalidomide and rituximab
<b>Other recommended treatment</b>	<b>AR</b>	• Acalabrutinib and rituximab

People under active surveillance continue to have tests to keep an eye on their lymphoma. They see their doctor every 2 or 3 months, or longer if the disease has been stable for a while. If symptoms arise, they'll begin treatment.

## Follow-up care

After initial treatment, your care team will evaluate your results to see how well the therapy worked. You may need additional treatment depending on what type of response you had to the initial treatment:

### Complete response

If tests can no longer detect lymphoma, you've had a **complete response** to initial therapy. A complete response is often called remission. The lymphoma can still return, but you may be able to stop treatment and receive active surveillance.

In the meantime, you'll continue to see your care team for follow-up tests. These tests look for signs that the lymphoma has returned. Typical tests and schedules are:

- **Physical exam and lab tests** every 3 or 6 months for at least 5 years, then once a year or when recommended by your doctor
- **CT imaging** of your chest, abdomen, and pelvis no more than twice a year for the first 2 years if recommended by your doctor

Early-stage MCL that has a complete response to treatment may still return later (relapse). If follow-up tests show that the lymphoma has relapsed, you'll need additional treatment.

### Partial response

A **partial response** to primary therapy means that the lymphoma has decreased in size but is still there.

If you have a partial response, additional treatment may be recommended to try to put the lymphoma into remission (complete response).

### Progression

Progression means MCL has continued to grow or spread even with treatment. You'll need additional treatment to get the lymphoma under control.

## Additional treatment

The choice of additional treatment depends on which treatment you had first. In general, if your earlier treatment was:

- **Only radiation therapy** then you'll likely need more aggressive additional treatment. See *Chapter 4: Treatment for advanced MCL*.
- **Chemoimmunotherapy with or without radiation therapy** then you'll probably need more aggressive therapy—the kind recommended for relapsed or refractory MCL. See *Chapter 6: Treatment for recurrent MCL*.

In certain cases, though, relapsed MCL can be treated with the same type of therapy recommended for advanced stage MCL. For such cases, see *Chapter 4: Treatment for advanced MCL*.

## Key points

- MCL in its early stages is found in fewer areas in the body. MCL is rarely diagnosed at these stages.
- Radiation therapy or less intense chemoimmunotherapy may be enough to control lymphoma growth in early-stage MCL. Some people have both therapies.
- Some people with early-stage MCL may not need treatment immediately, depending upon their age and health. Their doctors may choose to “watch” them instead.
- If symptoms begin, people with early MCL are re-evaluated. If necessary, they’ll begin treatment with radiation therapy or chemoimmunotherapy, or both.
- Early-stage MCL that has a complete response to treatment may still relapse later on.
- Early-stage MCL that partially responds to less intense treatment will need more aggressive treatment.
- Early-stage MCL that continues to grow or spread after treatment will need the kind of treatment recommended for relapsed or refractory MCL.

## Questions to ask

- How long do I have to decide about treatment, and is there a social worker or someone who can help me decide?
- Am I eligible for watch-and-wait?
- Do I have a choice of when to begin treatment? Can I choose the days and times of treatment?
- What follow-up care is needed after treatment?
- What are the chances of the lymphoma worsening or returning?



**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)**

# 6

## Treatment for recurrent MCL

- 39 Second-line therapy
- 41 Additional treatment
- 42 Supportive care
- 43 Advance care planning
- 44 Key points
- 44 Questions to ask

**If first-line treatment doesn't work or the lymphoma returns, other types of treatment are available. In addition to a number of effective, approved therapies, you can also look for a clinical trial that's recruiting patients like you.**

In many people, mantle cell lymphoma (MCL) improves with treatment, but then eventually comes back (relapses).

In other cases, first-line treatment may have no effect, or the lymphoma may even get worse. This is called refractory disease. It means the lymphoma didn't respond to therapy.

MCL that is refractory or has relapsed after first-line therapy can be treated with another (second-line) therapy.

## Second-line therapy

As with first-line therapy, the goal of second-line therapy is to achieve remission. Remission is when the signs and symptoms of lymphoma have disappeared.

The idea behind second-line treatment is to try a different strategy than first-line treatment. Treatment choices for relapsed and refractory MCL are affected by your previous therapy, age, overall health, and other diseases or conditions you may have.

### Preferred options

In recent years, clinical trials have shown that targeted therapy with one of the BTK inhibitors can be more effective than other therapies for relapsed or refractory MCL. So, preferred second-line treatment includes either acalabrutinib (Calquence) or zanubrutinib (Brukinsa). **See Guide 5.** If you've been prescribed one of these for second-line therapy, you may need to continue taking it indefinitely or until MCL relapses again.

**“Just look around you. Sometimes it's easy to forget that you are surrounded by people who care about your well-being and success!”**



Another preferred second-line treatment is immunotherapy with lenalidomide (Revlimid) and rituximab (Rituxan).

Radiation therapy is sometimes used to treat MCL within a lymph node or other small area if it's causing troublesome symptoms like pain.

### Treatment options used in certain cases

Other drug combinations are useful in specific cases. Options for second-line treatments used in certain cases are listed in **Guide 5**.

#### Guide 5

#### Second-line treatment options for relapsed or refractory MCL

Preferred treatment options	• Acalabrutinib
	• Zanubrutinib
	• Lenalidomide and rituximab
Other recommended treatment	• Ibrutinib with or without rituximab
Treatments used in certain cases	• Bendamustine and rituximab <i>(Not recommended if you've been treated with bendamustine before)</i>
	• Dexamethasone, cytarabine, platinum-based chemotherapy, and rituximab <i>(Rituximab may be omitted if you've been treated with it before)</i>
	• Gemcitabine, oxaliplatin, and rituximab
	• Ibrutinib and venetoclax
	• Rituximab, bendamustine, and cytarabine <i>(Not recommended if you've been treated with bendamustine before)</i>
	• Venetoclax with or without rituximab

## Additional treatment

If second-line therapy appears to be working, then additional treatment may be able to get the lymphoma under even better control.

The type of additional treatment you receive is based on several factors. An important factor is how well second-line therapy treated the lymphoma. Other factors include your age, overall health, and which treatments you've already had.

### Guide 6

#### Additional therapy options for relapsed or refractory MCL

<b>BTK inhibitor</b>	<ul style="list-style-type: none"> <li>• Only if:               <ul style="list-style-type: none"> <li>• You haven't taken a BTK inhibitor before, or</li> <li>• You have taken a BTK inhibitor before, but will now be taking a different one (pirtobrutinib)</li> </ul> </li> </ul>
<b>Bispecific antibody</b>	<ul style="list-style-type: none"> <li>• Only if:               <ul style="list-style-type: none"> <li>• You've already had CAR-T cell therapy and pirtobrutinib (BTK inhibitor), or</li> <li>• You're ineligible for CAR-T cell therapy</li> </ul> </li> </ul>
<b>CAR T-cell therapy</b>	<ul style="list-style-type: none"> <li>• Only if you've already had chemoimmunotherapy and BTK inhibitor(s)</li> </ul>
<b>High-dose chemotherapy and autologous stem cell transplant</b>	<ul style="list-style-type: none"> <li>• Only in selected cases and only if you've never had a stem cell transplant before</li> </ul>
<b>Allogeneic stem cell transplant with or without radiation therapy</b>	<ul style="list-style-type: none"> <li>• Only if your MCL is in remission and you've already had CAR-T cell therapy</li> </ul>
<b>Clinical trial</b>	<ul style="list-style-type: none"> <li>• People who have relapsed or refractory MCL are strongly encouraged to try to enroll in a clinical trial</li> </ul>
<b>Radiation therapy</b>	<ul style="list-style-type: none"> <li>• Low-dose radiation therapy can be used to relieve pain symptoms</li> </ul>
<b>Additional supportive care</b>	<ul style="list-style-type: none"> <li>• For relieving lymphoma symptoms and the side effects of lymphoma treatment, and also for psychological, social, and spiritual issues.</li> </ul>

Third-line and further therapies generally include any treatment for MCL that you haven't already had. These may include the BTK inhibitor pirtobrutinib (Jaypirca), CAR T-cell therapy with brexucabtagene autoleucel (Tecartus) or lisocabtagene maraleucel (Breyanzi), or the bispecific antibody glofitamab-gxbm (Columvi).

For example, if your second-line treatment was immunotherapy with lenalidomide and rituximab, your next treatment may be a BTK inhibitor.

Or, if you're taking a BTK inhibitor as your second-line treatment but it's losing its effect, you might begin to take pirtobrutinib instead. Pirtobrutinib is also a BTK inhibitor but it works in a slightly different way than other BTK inhibitors.

Another option: NCCN experts strongly encourage people with relapsed or refractory MCL to ask their health care team how to find a relevant clinical trial.

These and other options for additional therapy are listed in **Guide 6**.

Information about the side effects of CAR T-cell therapy is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](https://www.nccn.org/patientguidelines) app.

## Follow-up care

After treatment, you'll need to see your care team frequently so they can check how you're doing. You'll likely have follow-up visits every 3 to 6 months or as often as your care team recommends.

Follow-up tests often include in-person check-ups to evaluate how you feel, as well as evaluations such as a physical exam, blood tests, and imaging tests (CT scans). The follow-

up plan is adapted for each person and can be adjusted for someone who's in a long remission (for example, less frequent follow-up visits).

## Supportive care

Supportive care is for relieving the symptoms of lymphoma and the side effects of lymphoma treatment. It's also for other issues related to lymphoma.

For people with relapsed or refractory MCL, an important type of supportive care may be radiation therapy to relieve pain. Low-dose radiation therapy is not given to cure the lymphoma but can alleviate symptoms such as bone pain. For other types of pain, you may receive medicine or other treatment.

There's also treatment available for mouth sores and swelling (oral mucositis), which is a side effect of some lymphoma therapies.

Supportive care can also help with psychological, social, and spiritual issues. Ask your care team what supportive care resources are available to help you.

Living with lymphoma is called survivorship. It starts when your lymphoma is diagnosed. Read more about survivorship in *NCCN Guidelines for Patients: Survivorship Care for Cancer-Related Late and Long-Term Effects*, available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](https://www.nccn.org/patientguidelines) app.

## Advance care planning

When lymphoma is diagnosed very late or keeps progressing despite all treatment efforts, it may be time to consider what lies ahead. This exploration of what's important to you is called advance care planning.

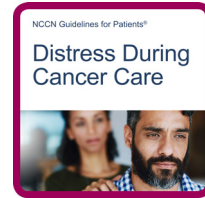
Advance care planning is for anyone with lymphoma, not only for those who are very sick. Even when lymphomas are curable, talking about future scenarios should begin when starting treatment.

Advance care planning means deciding what care you would want if you become unable to make medical decisions for yourself. It's about making sure that your wishes are understood and respected. The focus is on you receiving the best possible care at the end of your life. People with incurable lymphoma can set up an advance care plan early on to feel less stressed and better able to cope with their condition.

You can decide if there is a point where you might want to stop lymphoma treatment. You can also decide what treatments you would want for symptom relief.

If your family or loved ones disagree with your plan, speak to your care team. Sometimes they or other specialists can help you and your family navigate these difficult conversations.

You can change your advance care plan at any time. Frequent conversations with your care team can help.



### It's important to ask for help

Depression, anxiety, fear, and distress are very common feelings for people with lymphoma. These feelings can make it harder to deal with lymphoma and lymphoma treatment. They can hold you back even when you want to move forward. Getting help when you're feeling worried or hopeless is an important part of lymphoma care. If you're feeling anxious or overwhelmed, ask your treatment team for help.

More information about cancer and distress is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.

## Key points

- If first-line treatment doesn't work or the lymphoma relapses, you can have second-line treatment that uses a different strategy.
- Preferred options for second-line treatment include BTK inhibitors or immunomodulators.
- NCCN experts strongly encourage people with relapsed or refractory MCL to try to find a relevant clinical trial.
- Additional therapy can be used after second-line treatment to give it a boost or to get the lymphoma under control.
- Additional treatment, if appropriate, may include a different type of BTK inhibitor, CAR T-cell therapy, or a type of systemic therapy you haven't had before.
- Supportive care is an important part of your treatment care. It can help prevent or reduce the side effects of treatment, among other things.
- Supportive care and advance care planning aren't only for those who are very sick but for anyone with lymphoma and their loved ones.

## Questions to ask

- Does this hospital or cancer center offer the best treatment for my lymphoma?
- Are there any programs to help pay for treatment?
- What should I know if I need to travel for treatment?
- Who should I contact with questions or concerns during weekends or non-office hours?
- Do you recommend that I consider a clinical trial for treatment?

# 7

## Other resources

- 46 What else to know
- 46 What else to do
- 46 Where to get help
- 47 Questions to ask

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

## What else to know

This book can help you improve your care. It plainly explains expert recommendations and suggests questions to ask your care team. But it's not the only resource that you have.

You're welcome to receive as much information and help as you need. Many people are interested in learning more about:

- The details of their health and treatment
- Finding a health care practitioner who's experienced in lymphomas
- The side effects of lymphoma treatment
- How to get a second opinion
- Their chances for lymphoma recurrence
- Getting financial help

## What else to do

Your health care center can help you with next steps. They often have 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.

In addition to help from your health care team, the resources listed in the next section provide support for many people like yourself. Look through the list and visit the provided websites to learn more about these organizations.

## Where to get help

**Blood & Marrow Transplant Information Network (BMT InfoNet)**

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

**CancerCare**

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

**GRACE**

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

**Imerman Angels**

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

**Lymphoma Research Foundation**

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

**National Bone Marrow Transplant Link (nbmtLINK)**

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

**National Coalition for Cancer Survivorship**

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

**NMDP**

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

**Stupid Cancer**

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

**The Leukemia & Lymphoma Society**

[LLS.org/PatientSupport](http://LLS.org/PatientSupport)

**Triage Cancer**

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

## Questions to ask

- Who can I talk to about help with housing, food, and other basic needs?
- What help is available for transportation, childcare, and home care?
- What other services are available to me and my caregivers?
- 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?

A longer list of *Questions to Ask about Cancer Care* is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



**Hope is a huge part of the cancer process. Because if you lose that, you don't have the inner strength you need to fight.”**



## Words to know

### **active surveillance**

A period of testing for changes in cancer status while not receiving treatment.

### **additional treatment**

A shorter and more intense treatment phase to further reduce the number of cancer cells after primary treatment.

### **allogeneic stem cell transplant**

A cancer treatment that replaces abnormal blood stem cells with healthy donor cells. Also called allogeneic hematopoietic cell transplant.

### **autologous stem cell transplant**

A cancer treatment that removes a patient's own healthy stem cells and later returns them to the bone marrow after chemotherapy. Also called high-dose chemotherapy with autologous stem cell rescue (HDT/ASCR).

### **B cell**

A type of white blood cell (lymphocyte) that protects the body from infection. Also called B lymphocyte.

### **B symptoms**

Fevers, heavy sweats, and unexpected weight loss caused by B-cell lymphomas.

### **beta-2 microglobulin**

A small protein made by many types of cells.

### **biopsy**

A procedure that removes fluid or tissue samples to be tested for disease.

### **bispecific antibody**

A targeted therapy that binds to two different targets at the same time.

### **bone marrow**

The sponge-like tissue in the center of most bones.

### **bone marrow aspiration**

A procedure that removes a liquid bone marrow sample to test for a disease.

### **bone marrow biopsy**

A procedure that removes bone and solid bone marrow samples to test for a disease.

### **BTK inhibitor**

A drug that blocks an enzyme called BTK. Blocking BTK slows or stops cancer cells from growing.

### **cancer stage**

A rating of cancer based on its location and extent.

### **CAR T-cell therapy**

An immunotherapy that alters a person's own T cells to recognize and destroy their cancer.

### **chemotherapy**

Cancer drugs that stop the cell life cycle so cells don't increase in number.

### **chromosomes**

Structures within cells that contain coded instructions for cell function.

### **clinical trial**

A type of research that assesses how well health tests or treatments work in people.

### **complete blood count (CBC)**

A lab test that measures the number of red blood cells, white blood cells, and platelets.

**complete blood count (CBC) with differential**

A lab test that measures the number of blood cells including each type of white blood cell.

**complete response**

An absence of all signs and symptoms of cancer after treatment.

**comprehensive metabolic panel**

Lab test of up to 14 chemicals in your blood.

**computed tomography (CT)**

A test that uses x-rays from many angles to make a picture of the insides of the body.

**diagnosis**

An identification of an illness based on tests.

**early stage**

A cancer that has had little or no growth into nearby tissues.

**echocardiogram**

A test that uses sound waves to make pictures of the heart.

**gastrointestinal (GI) tract**

The group of organs through which food passes after being eaten. Also called the digestive tract.

**gene**

Coded instructions for making proteins that control how cells behave and make new cells.

**hematopathologist**

A doctor who examines cancers of the blood and immune cells.

**imaging**

A test that makes pictures (images) of the insides of the body.

**immune system**

The body's natural defense against disease.

**immunomodulator**

A cancer drug that modifies some parts of the body's disease-fighting system.

**immunotherapy**

A treatment with drugs that help the body find and destroy cancer cells.

**involved-site radiation therapy (ISRT)**

Treatment with radiation that's focused on areas with cancer growth.

**lactate dehydrogenase (LDH)**

A blood test that indicates the amount of lymphoma and cellular damage in the body.

**lumbar puncture**

A procedure that removes spinal fluid with a needle. Also called a spinal tap.

**lymph**

A clear fluid containing white blood cells.

**lymph node**

A small, bean-shaped, disease-fighting structure.

**lymphadenopathy**

A medical term meaning swollen lymph nodes.

**lymphatic system**

A network of organs and vessels that collects and transports lymph fluid.

**lymphocyte**

One of three main types of white blood cells that help protect the body from infections.

**lymphoma**

A cancer of white blood cells (lymphocytes) within the lymphatic system.

**maintenance treatment**

A treatment phase given to prolong good treatment results.

**mantle zone**

A ring of B cells that surrounds the germinal center of a follicle inside lymph nodes.

**medical history**

A report of all your health events and medications.

**monoclonal antibody**

A type of cancer drug that stops growth signals.

**multigated acquisition (MUGA) scan**

A test that uses radiation to make pictures of the heart.

**performance status**

A rating of a person's ability to do daily activities.

**positron emission tomography (PET)**

A test that uses radioactive material to see where lymphoma is located in the body.

**primary treatment**

The first treatment that is given to greatly reduce the extent of cancer.

**prognosis**

The likely course and outcome of a disease.

**radiation therapy**

A treatment that uses intense energy to kill cancer cells.

**refractory cancer**

Cancer that doesn't respond to treatment.

**relapse**

The return of cancer after a period of improvement.

**side effect**

An unhealthy or unpleasant physical or emotional response to treatment.

**spleen**

An organ on the left side of the body that helps prevent disease by filtering the blood.

**supportive care**

Health care that includes symptom relief and improving quality of life. Also sometimes called palliative care.

**T cell**

A type of white blood cell (lymphocyte) that attacks infected cells and cancer cells.

**targeted therapy**

A drug treatment that targets specific molecules that keep cancer cells alive and growing.

**translocation**

The switching of parts between chromosomes.

**uric acid**

A chemical that is released into the blood when cells and other substances in the body break down.

**white blood cell**

A type of blood cell that fights disease and infection.

# NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas, Version 2.2025. 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 • [penmedicine.org/cancer](http://penmedicine.org/cancer)

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

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

**Dana-Farber/Brigham and Women's Cancer Center |  
Mass General Cancer Center**  
Boston, Massachusetts  
877.442.3324 • [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 Center**  
Seattle, Washington  
206.667.5000 • [fredhutch.org](http://fredhutch.org)

**Huntsman Cancer Institute at the University of Utah**  
Salt Lake City, Utah  
800.824.2073 • [healthcare.utah.edu/huntsmancancerinstitute](http://healthcare.utah.edu/huntsmancancerinstitute)

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

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

**Mayo Clinic Comprehensive 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 UChicago Medicine Comprehensive Cancer Center**  
Chicago, Illinois  
773.702.1000 • [uchicagomedicine.org/cancer](http://uchicagomedicine.org/cancer)

**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 F Diego 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 • [uclahealth.org/cancer](http://uclahealth.org/cancer)

## 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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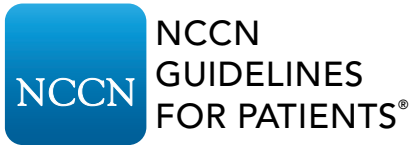
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