National Comprehensive Cancer Network®

2026

NCCN Guidelines for Patients®

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

Chronic Lymphocytic Leukemia

Presented with support from NCCN FOUNDATION® Guiding Treatment. Changing Lives.

Available online at NCCN.org/patientguidelines

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 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2026—October 10, 2025.

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Contents

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1
About CLL

Chronic lymphocytic leukemia (CLL) is a type of blood cancer that usually grows slowly. Treatment may not be needed for years, and some people may never need it. Most people will need treatment at some point though, and newer treatments can help extend life.

What's in this guide?

This patient guide describes everything you need to know about living with CLL, including:

- Tests needed to figure out the best treatment for you
- A period of monitoring, known as watch and wait
- Treatments available for CLL
- Caring for a rare complication called Richter's transformation
- Supportive care to improve your quality of life

What is CLL?

Chronic lymphocytic leukemia (CLL) is a cancer that affects your lymphocytes, which are a type of white blood cell.

CLL stands for:

- **Chronic** – a condition that occurs for a long time
- **Lymphocytic** – refers to lymphocytes, a type of white blood cell affected by the cancer
- **Leukemia** – a cancer that occurs in blood cells

Your blood contains several types of blood cells. One of those is white blood cells. B cells, also called B lymphocytes, are one type of white blood cell. They're made in the bone marrow, which is the soft, spongy tissue inside most of your bones. When they've appropriately matured, B cells leave your bone marrow to work in your bloodstream.

In people with CLL, abnormal B cells multiply and grow out of control. Because there are so many abnormal B cells, the healthy B cells are crowded out and aren't able to do their jobs effectively. This results in fewer healthy blood cells and a higher risk for infection.

How is CLL treated?

Treatment for CLL depends on your body. Most people don't need it right away. Depending on your symptoms and test results, starting treatment early may not help. When this is true, a watch-and-wait approach is used, which is when your care team monitors your CLL and checks on your health. Watch and wait is described in *Chapter 3: Figuring out when to start treatment*.

But treatment may be needed if you have low amounts of certain blood cells, which is called cytopenia. This includes low numbers of healthy red blood cells (anemia) and low numbers of platelets (thrombocytopenia) that don't get better with treatment.

Treatment may also be needed if the cancer is spreading, if it's bigger than a specific size, if there is a risk for significant organ damage, or if you have the following symptoms:

- Severe tiredness (fatigue)
- Night sweats
- Fever when you don't have an infection
- Significant unintentional weight loss

Treatment can also be given if a clinical trial is available for you. A clinical trial is a type of medical research study that is described in *Chapter 4: Types of treatment*.

Many treatment options are available and should be discussed with your doctor as your condition is monitored. Treatments range from pills you take every day to a combination of intravenous (IV) infusions and pills taken for a specific amount of time. IV infusions are given using a needle that is inserted into one of your veins.

It's important to know that many people live with CLL for years without needing treatment. Each person is different, so treatment is given at different times based on what each person needs.

Who's on your care team?

Treating CLL takes a team approach. Some members of your care team will be with you throughout your treatment, while others will be there for parts of it. Your team should communicate and work together to bring the best knowledge from each specialty.

Your care team may include:

- **Medical oncologists**: doctors who specialize in prescribing cancer drugs. They are trained to diagnose and treat cancer using special medicine.
- **Hematologists**: doctors who are experts in blood diseases and cancers.
- **Pathologists and hematopathologists**: doctors who are trained to study blood diseases involving different organs.
- **Oncology nurses**: nurses who provide hands-on care, like giving certain therapy, managing your care plan, answering questions, and helping you cope with side effects.
- **Other specialists**: this can include pharmacists, physician assistants, patient navigators, and social workers.

Today, there is no cure for CLL, but treatments can help control its symptoms and signs. The goal is to prevent CLL from causing problems and from becoming life-threatening.

You may have a more intense treatment plan if you develop Richter's transformation. This is a rare condition where CLL changes to become a more aggressive cancer. Richter's transformation is described in *Chapter 7: If CLL changes into another cancer: Richter's transformation*.

What is SLL?

Small lymphocytic lymphoma (SLL) and CLL are the same cancer, but the difference between the two is where the cancer cells are found. CLL is mainly found in the blood and bone marrow. SLL is most commonly found in lymph nodes (small, bean-shaped structures located throughout the body).

CLL can also be found in the lymph nodes and spleen, though. Your lymph nodes and spleen may be swollen because of a buildup of CLL or SLL cells. Importantly, these organs play a key role in fighting infections.

Treatment of CLL and SLL is the same because the cancer cells are the same. For this reason, the disease is often referred to as CLL/SLL. In this patient guide, treat any recommendation for CLL as a recommendation for SLL.

However, one exception is if you have stage 1 SLL. Stage 1 SLL is uncommon and is when the cancer's limited to 1 area of the body. It can be treated with radiation therapy, which may cure the disease.

"A diagnosis of CLL, like any cancer, can be scary. But the good news is there are now many treatment options and some people never need treatment. For most people, there's a long, high quality of life, ahead."

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.

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.

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.

2
Tests for CLL

You'll need specific tests to confirm that you have chronic lymphocytic leukemia (CLL). If CLL is found, you'll need more tests to decide if or when to start treatment, which treatment will work best, and what supportive care you'll need.

How is CLL confirmed?

Chronic lymphocytic leukemia (CLL) is usually diagnosed (identified and confirmed) with blood tests. Lymph node biopsies or bone marrow biopsies may also be done to help make a diagnosis.

Blood tests

Someone on your care team will take a small sample of your blood, which will be sent to a lab for testing. They'll take the sample by inserting a needle into one of your veins to remove the blood (this is called a blood draw).

A pathology doctor specialist, called a hematopathologist, is an expert at diagnosing cancers of blood cells. Hematopathologists look at blood, bone marrow, and lymph node samples for signs of disease. They'll do a test called a blood smear that examines your blood either under a microscope or with a machine. The way abnormal cells look can be a clue to which cancer you have.

Most cells have an identifiable pattern of proteins, like a shape, on their surface. This is called the immunophenotype. To identify specific proteins on white blood cells, the lab will do an immunophenotyping test using a method called flow cytometry.

The blood tests will also be used to get an absolute monoclonal B lymphocyte count, which checks certain white blood cell levels.

To be diagnosed with CLL, tests must show that you have at least 5,000 or more of the same white blood cells, called monoclonal B lymphocytes, per microliter of your blood. To be diagnosed with small lymphocytic lymphoma (SLL), the majority of the cancer must be found in the lymph nodes and tests must show less than 5,000 of those cells per microliter in your blood.

Additionally, people with SLL may have swollen lymph nodes (lymphadenopathy), a larger-than-normal spleen (splenomegaly), or both. An SLL diagnosis will be confirmed by a lymph node biopsy, which is explained next.

Diagnosis vs. prognosis

What's the difference between your diagnosis and your prognosis? These 2 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.

Biopsies

A biopsy is a procedure that removes samples of cells, fluid, or tissue from the body for testing. You may get a biopsy of your lymph nodes or bone marrow to confirm that you have CLL.

An excisional biopsy removes a whole lymph node, while an incisional biopsy removes part of a lymph node. Core needle biopsies take a small sample of a lymph node using a needle. Needle biopsies are done when lymph nodes are difficult to remove or when other biopsies are unsafe.

A bone marrow biopsy may be required in uncommon cases. This biopsy removes a sample of solid bone marrow tissue, and a bone marrow aspiration removes liquid bone marrow. Both bone marrow samples are usually taken at the same time from the back of the hip bone. After the samples are taken, they're sent to a lab for testing.

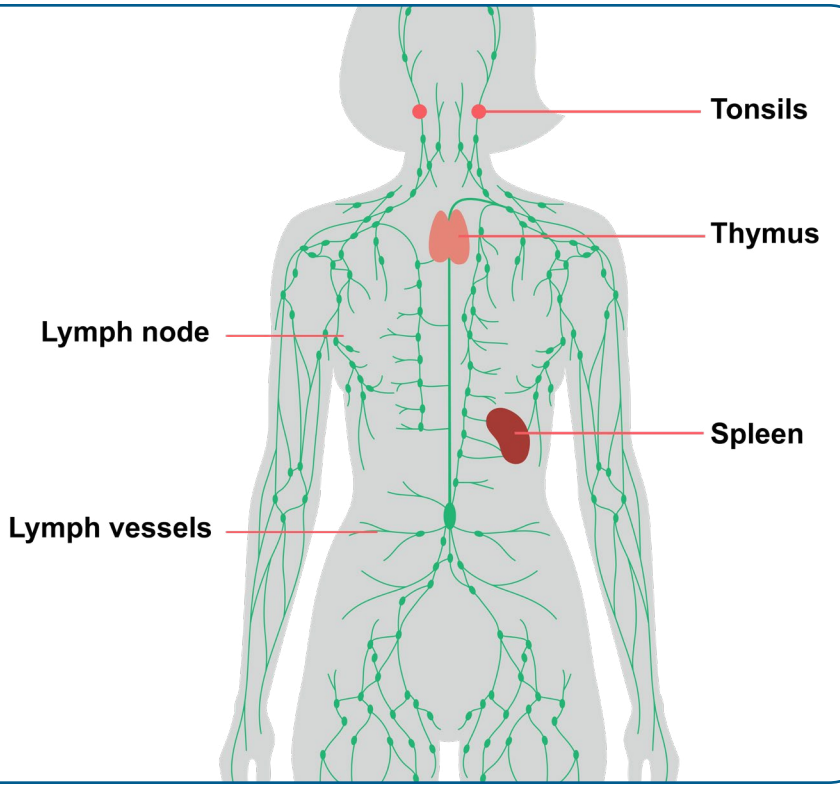
What happens after CLL is confirmed?

After you're diagnosed with CLL, lab test results are used to help plan your treatment. The lab results that are used for diagnosis are included in a pathology report, which will be sent to your hematologist-oncologist.

A **hematologist-oncologist** is an expert in blood cancers and will review the pathology report results with you. You may also be able to see the report through an online patient portal, or you can ask for a copy.

Lymphatic system

There are many B cells in the lymphatic system. This system plays a key role in fighting infections. The spleen, lymph nodes, lymph vessels, tonsils, and thymus are parts of the lymphatic system (shown). There are hundreds of lymph nodes in the body, and many are in the neck, armpits, and groin.



Treatment planning

The tests used to help plan treatment for CLL are listed in **Guide 1** and are described next. Tests that might be useful in some cases are detailed later in this chapter in **Guide 2**.

Medical history

Your care team needs to have all of your health information. They'll ask you about any health problems and treatments you've had during your lifetime. A complete report of your health is called a medical history. When you meet with your care team, be ready to talk about your:

- Family history
- Health conditions, illnesses, infections, and injuries
- Medications and supplements
- Drug allergies
- Surgeries and blood transfusions
- Lifestyle choices, like your diet, how active you are, and whether you smoke cigarettes or drink alcohol

They'll also ask if you're having any symptoms and complications. People with CLL may experience **B symptoms**. B symptoms are a general term used to describe the 3 symptoms of fever, night sweats, and unexplained weight loss. These symptoms can affect people with autoimmune disorders, cancer, and other conditions.

Additionally, some cancers and other health problems can run in families. Be prepared to discuss the health of your close blood relatives, like your siblings, parents, and grandparents. You're more likely to develop CLL if a close relative has it.

Guide 1
Tests used to plan treatment for CLL

Medical history, including B symptoms and family history
Physical exam, including the lymph nodes, spleen, and liver
Performance status score
Blood tests: • Complete blood count (CBC) with differential • Comprehensive metabolic panel
Biomarker tests: • FISH testing for chromosome changes (17p deletion, 13q deletion, 11q deletion, and trisomy 12) • DNA sequencing for the *TP53* mutation and *IGHV* mutation • Karyotype • Beta-2 microglobulin levels
Check for distress

Physical exam

A physical exam is performed to look for signs of disease. It's also used to help determine what treatments may be options for you. During this exam, your doctor or health care professional may:

- Check your vital signs—blood pressure, heart rate, breathing rate, and body

temperature—and assess your physical appearance

- Feel and listen to your organs, including your lymph nodes
- Assess your level of pain, if any, when you are touched

Checking for swelling

Cancer cells can build up in lymph nodes, the spleen, and the liver, causing them to swell. Your doctor will look at and gently press on your body to assess and measure the sizes of these organs. Areas that may be touched include your neck, armpit, belly, and groin.

Performance status score

Performance status is your ability to do daily activities, such as feeding yourself or bathing. Your oncologist will rate your performance status based on your health history and exam.

More blood tests

Blood tests can be used for diagnosis, but they can also measure blood cells, proteins, and other substances in the bloodstream. Tests that may be done with your blood sample include:

CBC with differential

A complete blood count (CBC) measures parts of the blood, including white blood cells, red blood cells, and platelets. A differential counts the number of each type of white blood cell.

People with CLL often have high counts of white blood cells and low counts of red blood cells and platelets.

Comprehensive metabolic panel

A comprehensive metabolic panel is used to diagnose, check for, and monitor different health conditions. It includes tests for 14 chemicals in the blood.

Biomarker tests

CLL cells have unique features that can be used to plan treatment specifically for you. These features are called biomarkers. Specific abnormal changes in your body's genes, such as genetic mutations or deletions, can also be biomarkers.

Different people can have different biomarkers, though, so a treatment that helps one person might not help you. That's why it's very important to have biomarker tests done and get a treatment plan that's specific to you.

Many different lab tests can be done to find biomarkers:

- Fluorescence in situ hybridization (FISH) can show changes in genetic material like missing parts and extra copies of chromosomes. For example, the FISH test can detect biomarkers called 17p deletion, 13q deletion, 11q deletion, and trisomy 12.
- DNA sequencing is used to look for mutations in the *TP53* gene and the *IGHV* gene.
- A karyotype (picture of all of a cell's chromosomes) can show extra, missing, rearranged, or abnormal pieces of chromosomes. A **complex karyotype** is when the karytope shows 3 or more unrelated changes in more than 1 cell.

- A serum test is a type of blood test that can detect beta-2-microglobulin levels. High levels of beta-2-microglobulin can be a sign of a specific condition or cancer. Levels are also connected to how aggressive the CLL is likely to be.

Biomarkers that are used to select treatments are discussed in *Chapter 4: Types of treatment*.

Additional tests you might need

Some people may need more tests to help diagnose or better understand their CLL. **Guide 2** describes the additional tests you might receive.

Guide 2
Tests that might be useful to plan treatment for CLL

Quantitative immunoglobulins test • Measures the amount of a certain protein called immunoglobulin in your blood
Serum protein electrophoresis (SPEP) with serum immunofixation electrophoresis (SIFE) tests • Measures specific proteins in your blood
Reticulocyte count, haptoglobin, and direct antiglobulin test • Checks parts of your blood relating to red blood cells
Uric acid levels • Measures levels of a normal waste product called uric acid in your body
Lactate dehydrogenase (LDH) levels • Measures levels of an enzyme called LDH. High LDH levels could be a sign of tissue damage
Bone marrow aspirate and biopsy • Examines bone marrow and can help in certain situations with diagnosis
Chest/abdomen/pelvis CT scan with contrast • Imaging test that can be used for a diagnosis, if needed
Hepatitis B and C virus testing, if you might receive treatment
Whole-body FDG-PET/CT scan to direct lymph node biopsy, if your care team thinks the CLL might be changing into another cancer
Pregnancy testing, if certain therapy is planned

Pregnancy and fertility

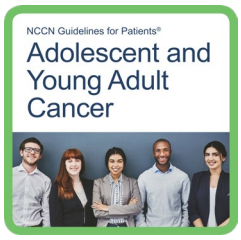
Some cancer treatments can harm an unborn baby. So if you have the potential to become pregnant, your cancer care team will give you a pregnancy test before you get treatment.

Some cancer treatments can also affect your ability to have a baby. Ask your care team if you're at risk for impaired fertility. It can happen to people of any gender.

Many people have healthy babies despite cancer and its treatment. If you wish to have children, there are steps to take before treatment. Even if you are unsure, talk to your care team.

You may be referred to a fertility specialist, who is an expert in helping people have babies. They can explain how you may be able to have a baby during or after treatment. Collecting and freezing sperm or eggs is a common method.

More information on fertility preservation can be found in the *NCCN Guidelines for Patients: Adolescent and Young Adult Cancer*, available at NCCN.org/patientguidelines, and on the NCCN Patient Guides for Cancer app.



Cancer treatment can impact one's ability to have children. Before starting treatment, talk with a fertility counselor to learn what your options are for fertility preservation.

Key points

- Results of blood tests and biopsies are often used to diagnose chronic lymphocytic leukemia (CLL).
- To plan treatment, your care team needs to know your health history and will examine your body. Tests will be done to learn if CLL is growing and affecting your organs.
- More blood tests and other types of tests will also be done. Some people need bone marrow biopsies or imaging, too.
- Your team may plan care based on the likely outcome of your cancer.
- Biomarker tests are important tests that are done to help plan treatment. They may also potentially inform your physician about prognosis.

Questions to ask

- Will my insurance pay for all of the tests you're recommending?
- Do I need to do anything to prepare for the tests?
- How soon will I know the results and who will explain them to me?
- How can I get a copy of the pathology report and other test results?

What's next?

What happens next depends on the results of your tests. You may move on to the watch-and-wait stage. This means you won't start any treatments for CLL, aside from those that make you feel better if you're sick. We'll talk more about this in *Chapter 3: Figuring out when to start treatment*.

But if your care team feels you need treatment, you could move on to it right away. Read about what treatments you could receive in *Chapter 5: Treating CLL*.

In uncommon cases, CLL can change into another cancer. When CLL turns into a different cancer, it's called Richter's transformation. *Chapter 7: If CLL changes into another cancer: Richter's transformation* describes the condition and treatments for it.

3

Figuring out when to start treatment

When you start treatment depends on whether treatment is needed. After your care team determines what stage of chronic lymphocytic leukemia (CLL) you have, they will know better if you should start treatment or wait. CLL isn't always treated right away, and some people will never need treatment. Your care team will check the cancer often and start treatment when it's needed. This approach is called watch and wait.

Staging the cancer

Staging is a method that oncologists use to describe how much cancer is in the body. Cancer can be at an early or a late (advanced) stage. The stage of your cancer is based on the results of your physical exam and the other tests that you had done.

Staging for CLL

The Rai staging system is commonly used for CLL. The Binet staging system is another option.

The Rai system consists of 5 cancer stages, ranging from stage 0 to stage 4. The stage of CLL you have depends on a few things: the amount of CLL lymphocytes you have; if your

Guide 3
Features people with each Rai stage have

	Rai stage 0	Rai stage 1	Rai stage 2	Rai stage 3	Rai stage 4
Many CLL lymphocytes	●	●	●	●	●
Enlarged lymph nodes		●	⊙	⊙	⊙
Enlarged spleen, liver, or both			●	⊙	⊙
Low numbers of red blood cells				●	⊙
Low numbers of platelets					●

● have ⊙ might have

lymph nodes are enlarged; if your spleen, liver, or both spleen and liver are enlarged; if you have low numbers of red blood cells; and if you have low numbers of platelets. **Guide 3** describes the features people with each Rai stage have.

The 5 stages can be condensed into 3 risk groups:

- Stage 0 has a low risk of needing treatment soon.
- Stages 1 and 2 have an intermediate risk of needing treatment soon.
- Stages 3 and 4 have a high risk of needing treatment soon.

Staging for SLL

The Lugano staging system is a similar staging system used for people with small lymphocytic leukemia (SLL). Stage 1 and 2 SLL means the cancer is at a limited stage and has not grown much. Stage 3 or 4 SLL means that the cancer is at a more advanced stage and has grown more.

When does treatment start?

When treatment starts is different for each person with CLL. You may not need treatment for CLL for months or years after being diagnosed. You may never need treatment. This is because, unlike other cancers, CLL usually grows very slowly. A term your care team might use is indolent (pronounced IN-doe-lent). Indolent cancer grows slowly.

Reasons for starting treatment are listed in **Guide 4**. You'll begin treatment after your care team finds out what stage of CLL you have and after all the tests needed to plan treatment are done. It's important to talk with your oncologist about starting treatment. Share your wishes and concerns. Together, you can decide when it's time to begin treatment.

Guide 4
Reasons to start treatment for CLL

• The cancer is spreading
• You can enroll in a clinical trial
• Your spleen or lymph nodes have gotten bigger than a certain size
• You have major symptoms of CLL as described in *Chapter 1: About CLL*
• CLL is causing 1 or more of your organs to stop working properly
• CLL is causing your red blood cell count to be low
• CLL is causing your platelet count to be low
• Your body isn't responding to treatment with steroids like it should

In general, oncologists recommend starting treatment if the cancer is spreading quickly or when the effects and symptoms of the cancer become worse than the risks of treatment.

Will I be okay without treatment?

Current research shows that delaying treatment is safe for many people. You and your care team may decide to delay treatment because:

- Treating CLL early on before symptoms get worse does not help you live longer.
- Treatment may cause unwanted health problems called side effects, which are inconvenient and may have out-of-pocket costs.
- There may be better treatments available in the future.

You can enroll in a clinical trial that assesses if early treatment is helpful for CLL. More research is being done to determine whether treatment should be delayed or started sooner.

What is watch and wait?

Watch and wait is a period where your care team will check on you and the CLL without giving you any treatment for CLL. They will closely monitor your condition by looking at blood counts and symptoms to see if there are any changes.

Watch and wait can go on for years. Your care team may call it active observation, active surveillance, or watchful waiting.

Meanwhile, you can take care of your health by:

- Going to your health appointments. Don't skip or put them off.
- Finding support. Watch and wait can cause worry or anxiety, and support groups or professional support may be helpful.
- Living a healthy lifestyle to improve your overall health.

See *Chapter 6: How supportive care can help you* for information that can help you during watch and wait. Chapter 6 explains recommendations for vaccines and care for cancer symptoms. It also describes other NCCN resources that can help improve your quality of life.

The key to managing fear is in making informed decisions. Stay positive, make a plan for yourself, and go forward one step at a time."

Key points

- Chronic lymphocytic leukemia (CLL) usually grows very slowly, so treatment may not be needed for months or years. Early treatment hasn't been shown to help people live longer.
- Your care team will regularly check on your CLL during the watch-and-wait period.
- During watch and wait, you can take care of your health by going to doctor's appointments, finding support, and living a healthy lifestyle.
- People with higher cancer stages are more likely to need treatment sooner than people with lower stages.
- Treatment is started based on advanced signs and symptoms of CLL.

Questions to ask

- What is my CLL stage? Does this stage mean my cancer is advanced?
- Do I have to start treatment right away?
- What can I do to be healthy if I don't need treatment right away?

4
Types of treatment

People with chronic lymphocytic leukemia (CLL) will receive targeted therapy. Treatment can be given over a set period of time or over many months or years. Clinical trials are also a treatment option. Chimeric antigen receptor (CAR) T-cell therapy, allogeneic hematopoietic cell transplant, chemotherapy, and PI3K inhibitors may also be given in certain situations.

About treatment for CLL

A team of experts will give you your cancer treatment and support you. Chronic lymphocytic leukemia (CLL) is treated with cancer medicine, which includes pills, capsules, or intravenous (IV) medicines (given through a needle or tube inserted into one of your veins). Sometimes, certain treatments can be injected just under the skin (subcutaneous). Most treatments consist of 1 or more drugs.

All treatments listed in this guide are recommended and appropriate. When helpful, NCCN experts also assign a level of preference to their recommendations for **systemic therapies** (drug therapies that treat the whole body):

- **Preferred therapies** have the most evidence they may work better and be safer than other therapies.
- **Other recommended therapies** can provide effective results but may have less evidence, more side effects, or may not work quite as well as preferred therapies.
- **Therapies used in certain cases** work best for individuals with specific cancer features or health circumstances.

People with CLL are often treated over the course of their lives with a series of different treatments. The first treatment given is called first-line therapy. Second-line therapy is the second treatment given, and so on.

Treatments can cause unwanted health problems called side effects. Side effects vary from person to person. Ask your care team for a list of your treatments' possible side effects. Also, tell your team about any new or worsening symptoms you have. There may be ways to help you feel better. Care and treatments for side effects are explained in *Chapter 6: How supportive care can help you*.

> **"I found tremendous comfort in focusing on the things that I could control, such as taking medications as directed, taking an active role in educating myself about my disease and my treatment plan, and ensuring I asked for (and received) proper care."**

Will I need tests before treatment?

The cancer will be tested before each line of treatment because CLL may change during watch and wait and after treatment starts.

Your care team will look at your:

- Fluorescence in situ hybridization (FISH) testing results for the 17p deletion
- *TP53* mutation status
- *IGHV* mutation status (*IGHV* mutation status only needs to be tested once because it will not change over time)
- Karyotype

They will also do:

- Imaging, if needed
- A bone marrow aspirate and biopsy, if needed

For more information about these tests and testing in general, see *Chapter 2: Tests for CLL*.

How long will I need treatment?

How long you receive treatment for depends on the therapy you get and whether it's time limited or continuous. These are the 2 different ways that people with CLL can receive treatment. Which treatment you'll receive depends on many factors. Your care team will go over the options.

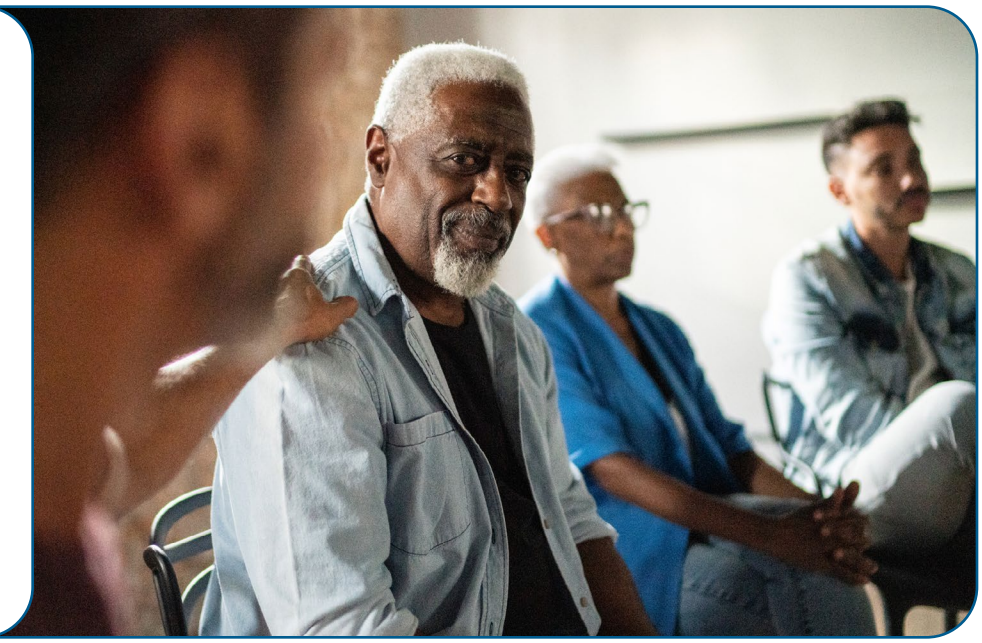
Time-limited treatment is:

- Given for a specific period of time

Continuous treatment is:

- Given over many months or even years with no set endpoint

You're not alone. Ask your care team about support groups in your area.



Targeted therapies

Targeted therapies are the most common treatment for CLL. These therapies are drugs that find and attack specific cancer cells. They target a unique feature of the cell, such as a biomarker, to stop or block the cancer from growing and spreading.

Your oncologist will recommend a treatment based on several factors. Biomarker testing is essential. Your age, overall health, and other medications are also important factors when picking a treatment.

BCL-2 inhibitors

BCL-2 inhibitors are medications that target the BCL-2 family of proteins. The only BCL-2 inhibitor that is currently approved to treat CLL is venetoclax (Venclexta). Venetoclax is an oral medication that is taken as tablets.

Anti-CD20 monoclonal antibodies

Anti-CD20 monoclonal antibodies are medicines that target the CD20 protein. Rituximab (Rituxan) and obinutuzumab are anti-CD20 monoclonal antibodies used to treat CLL. Both of these medicines can be given using an IV or subcutaneous injection.

BTK inhibitors

BTK inhibitors are oral medications that target a protein called Bruton's tyrosine kinase (BTK). There are 2 types of BTK inhibitors—covalent and non-covalent—which work in different ways. The kind of BTK inhibitor given depends on the situation. Covalent BTK inhibitors are more commonly used to treat CLL.

The recommended BTK inhibitors to treat CLL include the covalent BTK inhibitors acalabrutinib (Calquence), zanubrutinib (Brukinsa), and ibrutinib (Imbruvica) and the non-covalent BTK inhibitor pirtobrutinib (Jaypirca). Some of these BTK inhibitors are given alone, while others are given in combination with other therapies.

Other treatments you might receive

If you've already received treatment and it isn't working or has stopped working, you have more options available. PI3K inhibitors, chemotherapy, CAR T-cell therapy, and allogeneic hematopoietic cell transplant may be options for people who have already received treatment.

PI3K inhibitors

PI3K inhibitors are another type of targeted therapy. They aren't used as commonly as other targeted therapies for CLL, but they can be used in certain cases. PI3K inhibitors include duvelisib (Copiktra) and idelalisib (Zydelig).

Chemotherapy

Chemotherapy kills fast-growing cells like cancer. Fludarabine and cyclophosphamide are 2 chemotherapies that are given together in combination with the targeted therapy rituximab. Bendamustine is another chemotherapy you might receive.

CAR T-cell therapy

CAR T-cell therapy is a personalized type of immunotherapy. It uses your own immune system to fight cancer.

Allogeneic hematopoietic cell transplant

An allogeneic hematopoietic cell transplant uses healthy blood-forming cells (stem cells) from another person (donor) to treat your cancer.

To get a hematopoietic cell transplant, you must not have any significant health problems besides cancer. Most people with CLL don't get a transplant.

Clinical trials

Another way to receive treatment for CLL is by participating in a clinical trial, if one is available and is the right fit.

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. 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.

Finding a clinical trial

In the United States

NCCN Cancer Centers
NCCN.org/cancercenters

The National Cancer Institute (NCI)
cancer.gov/about-cancer/treatment/clinical-trials/search

Worldwide

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

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.

- **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, the FDA may approve it.
- **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 almost never used alone in cancer clinical trials. It is common to receive either a placebo with a standard treatment, or a new drug with a standard treatment. You'll be informed, verbally and in writing, if a placebo is part of a clinical trial before you enroll.

Are clinical trials free?

There's 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 cancer care. This care is often covered by insurance.

Therapy for Richter's transformation

Chemoimmunotherapy may be given if you have Richter's transformation, as described in detail in *Chapter 7: If CLL changes into another cancer: Richter's transformation*.

Chemoimmunotherapy is the combination of chemotherapy and immunotherapy treatments. Chemotherapy kills cancer cells, and immunotherapy enables your immune system to fight cancer. Rituximab is given as part of the chemoimmunotherapy treatment for Richter's transformation. Even though rituximab is a targeted therapy, it is also an immunotherapy because it uses your body's immune system to help fight cancer.

Chemoimmunotherapy and immunotherapy are given in cycles. A cycle is a period of days of treatment followed by days of rest. Chemoimmunotherapy can be given by IV infusion, and some drugs may even be given as injections or oral pills.

Key points

- You'll have tests done before each treatment you receive.
- People with chronic lymphocytic leukemia (CLL) are treated with a targeted therapy. Targeted therapies used to treat CLL include drugs that are BCL-2 inhibitors, anti-CD20 monoclonal antibodies, and BTK inhibitors.
- Some treatments can be time limited (given over a set period of time) or continuous (given over many months or years).
- Additional treatment options are clinical trials, chimeric antigen receptor (CAR) T-cell therapy, allogeneic hematopoietic cell transplant, chemotherapy, and PI3K inhibitors. These treatments are given in certain cases.

Questions to ask

- How do my age, overall health, and other factors affect my treatment options?
- What can I expect from treatment?
- What clinical trial options are available?
- Are there resources to help me pay for treatment or other care I might need?

5
Treating CLL

Your treatment plan will be designed specifically for you. The first treatment given for chronic lymphocytic leukemia (CLL) includes different combinations of targeted therapy drugs. If you need a second treatment, it will be chosen based on how the first one worked. There are many options after the second treatment as well.

First-line therapies for CLL

First-line therapy means the first therapy you're given. For people with chronic lymphocytic leukemia (CLL), the first treatment is usually targeted therapy. Targeted therapy works by blocking the growth and survival of certain CLL cells.

There are many treatment options for CLL, but some are more commonly used than others. Treatment for many people starts with time-limited therapy (given for a set period of time). This type of therapy is given either with a BCL-2 inhibitor plus an anti-CD20 monoclonal antibody, or a BCL-2 inhibitor plus a covalent BTK inhibitor with or without an anti-CD20 monoclonal antibody. Some people start treatment with continuous therapy (given over many months or years). People receiving continuous first-line treatment may receive a covalent BTK inhibitor with or without an anti-CD20 monoclonal antibody.

Many times, drugs are combined and given together as part of your **treatment regimen**. A treatment regimen is a plan that specifies the dose, schedule, and duration of treatment. **Guide 5** lists the available treatment regimens for first-line CLL therapy. The treatment you get depends on if you have a 17p deletion or *TP53* mutation.

Which treatment regimen is best for you?

Your care team will choose a treatment with you based on many factors. Before starting treatment with a BTK inhibitor, your oncologist may check to see if you are at risk for heart (cardiovascular) disease. In uncommon cases, BTK inhibitors can cause heart problems.

Some people may also want a treatment with a fixed duration, while others may prefer a continuous one. Another thing many people want to know is whether treatment is given as pills you can take at home or given using an IV. Your care team will also examine the side effects of each drug. Talk with your care team to figure out which treatment would work best for you.

Checking treatment responses

To find out how well your treatment is working, you'll need to have tests done to check how the cancer has responded to treatment. These tests include an updated medical history, a physical exam, blood tests, and, sometimes, imaging.

Guide 5
First-line treatment options for CLL

Type of treatment	Therapies in the treatment regimen	CLL without 17p deletion and *TP53* mutation	CLL with 17p deletion or *TP53* mutation
BCL-2 inhibitor plus anti-CD20 monoclonal antibody	**Venetoclax plus Obinutuzumab (fixed duration)**	Preferred regimen	Preferred regimen
Covalent BTK inhibitor with or without anti-CD20 monoclonal antibody	**Acalabrutinib (continuous) with or without Obinutuzumab**	Preferred regimen	Preferred regimen
Covalent BTK inhibitor	**Zanubrutinib (continuous)**	Preferred regimen	Preferred regimen
BCL-2 inhibitor plus covalent BTK inhibitor with or without anti-CD20 monoclonal antibody	**Venetoclax plus Acalabrutinib with or without Obinutuzumab**	Preferred regimen	Preferred regimen (everyone will receive Obinutuzumab)
BCL-2 inhibitor plus covalent BTK inhibitor	**Venetoclax plus Zanubrutinib**	Regimen is useful in certain circumstances	Preferred regimen
BCL-2 inhibitor plus covalent BTK inhibitor	**Venetoclax plus Ibrutinib (fixed duration)**	Other recommended regimen	Other recommended regimen

Types of responses

Based on the results of the tests, your response to treatment will be one of the following:

- Complete remission: There are no signs of CLL.
- Partial remission: The amount of CLL has decreased, and the cancer is not growing.
- Stable disease: The cancer has not gotten worse, but it also hasn't gotten better.
- Progressive disease: The cancer is still growing.

CLL that is not in remission

The next steps in treatment depend on how the cancer responds to treatment. Your treatment plan may not change if CLL is still the same. If CLL is growing, you'll likely start a different type of treatment. For some people, more tests are needed to plan treatment.

Testing for transformed CLL

If CLL is growing while you're getting any treatment, it may have transformed into a different type of cancer. CLL can change into a faster-growing cancer, which is described in *Chapter 7: If CLL changes into another cancer: Richter's transformation*. This doesn't happen often. Transformed CLL is confirmed by lab tests that are done on a biopsy sample.

CLL that is in remission

After you experience remission, your care team will check on the status of your CLL at regular follow-up visits. You may continue to receive treatment during remission.

Your medical history will be updated at these follow-up visits. You'll also have a physical exam and blood tests.

Testing for minimal residual disease

After treatment, your oncologist may want to test for minimal residual disease. After successful treatment, there may still be a tiny number of cancer cells left, even though none can be seen with a microscope. This small amount of cancer is called minimal residual disease.

Very sensitive lab tests are used to detect minimal residual disease. If the test shows that you have undetectable minimal residual disease, that means the test didn't find any CLL cells. There may be no CLL cells, or too few to find, even with the most sensitive test.

Relapse

If CLL comes back after you are in remission for at least 6 months, it's called a relapse. Signs of a relapse can be swollen lymph nodes, a larger liver or spleen, and a significant increase in the number of lymphocytes.

If a relapse happens, treatment is started when there are signs that it's needed.

If the relapse occurs after remission, venetoclax (Venclexta) with or without obinutuzumab or another anti-CD20 monoclonal antibody is a treatment option. Venetoclax can also be given with a covalent

BTK inhibitor, or venetoclax can be given alone as a continuous treatment. People who have been given both a covalent BTK inhibitor treatment regimen and a BCL-2 therapy regimen can also receive all of the therapies listed in **Guide 7** later in this chapter.

Second-line therapies for CLL

Sometimes CLL can come back (relapse) or stop responding to treatment (refractory disease). So, many people will need different treatments over time.

The second treatment you will get is based on the results of prior treatments. Often, treatment is switched from a BTK inhibitor to a BCL-2 inhibitor, or the other way around. See **Guide 6** for a list of second-line treatments.

If treatment causes uncomfortable side effects, the treatment is often switched. A different therapy may have less severe side effects.

Importantly, pirtobrutinib (Jaypirca) is a different type of BTK inhibitor than the ones that can be given as first-line therapy. Pirtobrutinib is a non-covalent BTK inhibitor that can be given as second-line therapy if CLL did not get better, or if you couldn't take one of the first-line regimens that used a covalent BTK inhibitor.

Guide 6
Second-line treatments for CLL (with or without 17p deletion and *TP53* mutation)

Treatments with	Treatment regimen	Preference for the treatment
BCL-2 inhibitors	Venetoclax plus Obinutuzumab	Preferred regimen
	Venetoclax plus Rituximab	Other recommended regimen
	Venetoclax	Other recommended regimen
Covalent BTK inhibitors	Acalabrutinib (continuous)	Preferred regimen
	Zanubrutinib (continuous)	Preferred regimen
	Ibrutinib (continuous)	Other recommended regimen
Non-covalent BTK inhibitors	Pirtobrutinib (continuous)	Preferred regimen

After the second treatment

If you have already received treatment with a covalent BTK inhibitor and a BCL-2 inhibitor, additional treatments are available. These treatments are:

- Drug therapy with the treatments in **Guide 7**.
- Treatment with the chimeric antigen receptor (CAR) T-cell therapy lisocabtagene maraleucel (Breyanzi). Lisocabtagene maraleucel is sometimes called liso-cel.
- A clinical trial
  - Ask your care team if there's a clinical trial that's a good fit for you. For more information about clinical trials, go to *Chapter 4: Types of treatment*.
- Allogeneic hematopoietic cell transplant

Recommended drug treatments

- Pirtobrutinib is a non-covalent BTK inhibitor that is used by itself for treatment.
- Duvelisib (Copiktra) is a PI3K inhibitor that is used by itself to treat CLL. Another PI3K inhibitor, idelalisib (Zydelig), may be taken with or without rituximab (Rituxan).
- Alemtuzumab (Campath) is a CD52 monoclonal antibody used to treat CLL. It is a different type of monoclonal antibody from the anti-CD20 monoclonal antibodies rituximab and obinutuzumab. Alemtuzumab targets the CD52 protein instead of the CD20 protein like those drugs do. Alemtuzumab may be taken with or without rituximab if you have a 17p deletion or *TP53* mutation.
- Lenalidomide (Revlimid) is an immunomodulatory drug for CLL that affects the immune system in multiple ways. It's used by itself or with rituximab to treat CLL.
- Chemoimmunotherapy is an option for certain people with CLL. Fludarabine and cyclophosphamide are chemotherapies that are given with rituximab.
- Bendamustine is another chemotherapy that is given with rituximab, but it is given to people under the age of 65 years old. Importantly, these chemotherapies are not recommended for people with 17p deletions or *TP53* mutations.
- High-dose methylprednisolone (HDMP) is a corticosteroid that is given with either rituximab or obinutuzumab.

Guide 7
Treatments after covalent BTK inhibitors and BCL-2 inhibitors for relapsed or refractory CLL

Treatment	CLL
Lisocabtagene Maraleucel with or without Ibrutinib	Preferred regimen
Pirtobrutinib (if you haven't been treated with this yet) (continuous)	Preferred regimen
Duvelisib	Other recommended regimen
Idelalisib with or without Rituximab	Other recommended regimen
Lenalidomide with or without Rituximab	Other recommended regimen
Obinutuzumab	Other recommended regimen
Fludarabine and Cyclophosphamide plus Rituximab (FCR)*	Other recommended regimen
Alemtuzumab with or without Rituximab (if you have a 17p deletion or *TP53* mutation)	Other recommended regimen
Bendamustine plus Rituximab (if you are under 65 years of age) *	Other recommended regimen
High-dose Methylprednisolone (HDMP) with either Rituximab or Obinutuzumab (if you have a 17p deletion)	Other recommended regimen

***** not a treatment option if you have a 17p deletion or *TP53* mutation

Key points

- Before starting treatment, you'll need to be tested for any biomarkers that could affect your options. New biomarkers may appear during watch and wait or after first-line therapy.
- Ask your care team if there is a clinical trial that's a good fit for you. A clinical trial may be an option at any time during treatment.
- The first treatment for chronic lymphocytic leukemia (CLL) is often a combination of BTK inhibitors, BCL-2 inhibitors, and anti-CD20 monoclonal antibodies. These treatments control cancer growth well.
- If the cancer grows or you have severe side effects, the type of treatment is often switched. You may switch to a BTK inhibitor after having a BCL-2 inhibitor or the other way around.
- If first or second treatments stop working, you may have the option of a hematopoietic cell transplant, a recommended drug treatment, or chimeric antigen receptor (CAR) T-cell therapy.

Questions to ask

- What treatment is best for me and why?
- What are the possible complications and side effects of treatment?
- Are there any long-term or permanent side effects?
- Do any medications worsen side effects?
- Do you recommend that I consider a clinical trial for treatment?

6

How supportive care can help you

The goal of supportive care is to maintain or improve your quality of life. It's used to prevent or relieve health problems caused by chronic lymphocytic leukemia (CLL) or its treatment. Supportive care can also help with other needs, such as paying for care, getting transportation to care, and more.

What is supportive care?

Supportive care is an important part of cancer care. The goal is to improve your quality of life during and after cancer treatment. Supportive care is for everyone with cancer and their families, not just for those at the end of life. It's also known as palliative care.

Supportive care includes a wide range of services. Supportive care prevents or manages the symptoms of cancer and the side effects of cancer treatment, like pain and cancer-related fatigue. It also addresses the mental, social, emotional, and spiritual concerns faced by people with cancer.

Supportive care provides help with additional needs, such as:

- Making treatment decisions
- Coordinating your care
- Paying for care
- Planning for advanced care and end of life

Supportive care for CLL can help with:

Keeping you healthy

- Vaccines can help protect you from infections and other illnesses. Even if you aren't getting treatment for CLL at the moment, it's important to stay up-to-date on vaccines.
- Staying up-to-date on other cancer screenings is also important. People with CLL are at higher risk for getting another cancer. Your care team can help make sure you get the screenings you need.

Managing common side effects

- Supportive care can help you manage side effects that you might experience.
- Side effects your care team may pay extra attention to are:
  - CLL-related infections
  - Autoimmune cytopenias
  - Tumor lysis syndrome
  - Tumor flare
  - Blood clots
  - Bleeding and bruising

Assisting you in other ways

- Providing emotional support
- Getting you information that may be helpful. NCCN has many guides that focus on the treatment of common physical and emotional effects of many cancers.

Read more about the types of support you may receive in *NCCN Guidelines for Patients: Palliative Care*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Protecting yourself from infections with vaccines

You can protect yourself by staying up-to-date on certain vaccines. Vaccines help prevent infections by training your body to recognize and quickly attack germs.

Get recommended vaccines

Vaccines are proven to be safe and effective in preventing serious illnesses. Some vaccines are routine. Others are based on age, health, and other factors. Talk to your care team about which vaccines you need.

NCCN experts recommend these vaccines for people with CLL:

- The flu shot (influenza vaccine) every year, but only a non-live type
- Pneumococcal vaccine, as recommended by the U.S. Centers for Disease Control and Prevention (CDC)
- COVID-19 vaccine, as recommended by your care team following the CDC vaccination recommendations

Get the vaccines recommended by your oncologist. They will help protect you against infections.

- Non-live (recombinant) zoster vaccine to prevent shingles if you're being treated with a BTK inhibitor
- RSV (respiratory syncytial virus) vaccine

Avoid live vaccines

You should not get any live vaccine. Live vaccines contain a germ that has been weakened (attenuated), and they create a strong immune response to the real germ. Live vaccines may cause major health problems in people with weaker immune systems.

CLL-related infections

Cancer treatments weaken the body's immune system, which can make it harder for your body to fight off germs and infections. Weakened immunity can also make typical infections more severe. These infections that happen more often and are more severe are called opportunistic infections.

Preventing infections

Medicines used to treat infections can also be used to prevent them. The preventive care you might receive depends on the type of treatment you had or are having for CLL. Some cancer treatments weaken the immune system more than others.

Herpes and fungal pneumonia

Preventive care for herpes and fungal pneumonia is recommended during and after treatment with alemtuzumab (Campath), PI3K inhibitors, and certain chemoimmunotherapy treatments (such as with bendamustine). Acyclovir is an antiviral drug used to treat and prevent infections caused by herpes viruses.

Trimethoprim-sulfamethoxazole (Sulfatrim, Bactrim) is a medicine that is used to prevent *Pneumocystis jirovecii* pneumonia (PJP). PJP is a lung infection caused by a fungus.

If you're receiving a BTK inhibitor and are at higher risk of getting an opportunistic infection, your oncologist will provide preventive care and check on you to make sure you don't have an infection. The medicine used to prevent PJP may be given, and the varicella-zoster virus vaccine may also be given. The varicella-zoster virus causes chickenpox, and when reactivated in older people, shingles.

White blood cell-related infections

While taking venetoclax (Venclexta), levels of white blood cells called neutrophils can drop (a condition known as neutropenia). When levels of neutrophils are low, you're more likely to get infections. You'll need regular blood tests during treatment to check on your neutrophil levels. To help prevent infections caused by neutropenia, you may be given drugs called growth factors, antifungal drugs, or fluoroquinolones (a type of antibiotic medicine).

Hepatitis

If you've had hepatitis B, it may come back during cancer treatment. Entecavir (Baraclude) is the preferred medicine for preventing and treating hepatitis B. Other options are adefovir (Hepsera), telbivudine (Tyzeka), and tenofovir (Viread). Your care team will check on you throughout your cancer treatment if you have hepatitis B, and preventive care may continue for up to 12 months after CLL treatment ends.

Additionally, CLL is a type of non-Hodgkin lymphoma, and there's a link between hepatitis C and non-Hodgkin lymphoma. Direct-acting antiviral drugs can safely treat hepatitis C and may reduce the risk of lymphoma.

Cytomegalovirus

If you've had cytomegalovirus (CMV), there's a high risk that CMV will be reactivated if you're treated with a PI3K inhibitor or alemtuzumab. Screening for reactivation should be done at least every 4 weeks. The antiviral drug ganciclovir can help stop CMV from coming back.

Treating sinus and lung infections

Sometimes people with CLL get serious infections in their sinuses and lungs. Your oncologist will give you an antimicrobial drug, such as an antibiotic, to treat these infections.

Immunoglobulin also helps fight infections, so if your body isn't making enough of it, you may get immunoglobulin. Intravenous (IV) immunoglobulin (IVIG) can be given every month to help. It's given through a needle placed in your arm, or you can get injections under the skin every week (subcutaneous).

Could I get a second cancer?

People with CLL are at higher risk of getting another cancer, including melanoma or other skin cancers, so regular cancer screening is important. It is recommended that you see a dermatologist once a year for a skin exam. There are screening programs for prostate, breast, cervical, and colon cancers that are important to follow, too.

What's autoimmune cytopenia?

Autoimmune cytopenia is a condition where your immune system attacks your blood cells. There are several types of autoimmune cytopenias. The most common types among people with CLL are autoimmune hemolytic anemia, immune thrombocytopenic purpura, and pure red cell aplasia.

There are multiple treatment options for autoimmune cytopenias. Drug treatments include corticosteroids, rituximab (Rituxan), intravenous immunoglobulin, cyclosporine A, eltrombopag (Promacta), and romiplostim (Nplate). If steroids don't work or the cytopenia returns after treatment with steroids, BTK inhibitors may be used for treatment.

For some cytopenias, surgery may be an option. The spleen plays a key role in destroying platelets. So removing the spleen, called a splenectomy, can help get the number of platelets back to normal.

What's tumor lysis syndrome?

Several treatments for CLL kill many cells quickly, but when the waste released by dead cells is not quickly cleared out of the body, something called tumor lysis syndrome can happen. This may result in kidney damage and severe blood electrolyte disturbances. It can be life-threatening.

Your electrolyte levels will be checked often, and treatment will be given if needed. Tumor lysis syndrome may be prevented with hydration. Drink lots of water. You may also get fluid infused into your bloodstream to hydrate you. Medicines that lower uric acid levels can help, too. These medicines include allopurinol (Aloprim, Zyloprim), febuxostat (Uloric), or rasburicase (Elitek).

What's tumor flare?

Tumor flare is a fast, short-lived increase in cancer symptoms and cancer growth. Symptoms of tumor flare are swollen lymph nodes, swollen spleen, low fever, and rash. Treatment with lenalidomide (Revlimid) can cause tumor flare.

But steroids can prevent and treat tumor flare. Antihistamines are given if you have a skin rash and itchiness caused by the tumor flare.

Preventing and treating blood clots

A blood clot is a clump of blood that is gel-like or partially solid. Blood clots control bleeding, but they can also prevent blood flow, which can be dangerous.

Treatment with lenalidomide can sometimes cause blood clots, so if you are receiving lenalidomide, your doctor may recommend taking an anticoagulant (a medicine sometimes called a blood thinner).

Aspirin can also help prevent clots in some people. Importantly, aspirin is not needed if you are taking an anticoagulant drug like warfarin (Coumadin).

Monitoring bleeding or bruising

BTK inhibitors increase the risk of bleeding and bruising. Your oncologist will monitor your bleeding risk based on many factors. Regular blood tests are important because the risk of bleeding increases when your platelet count is low.

When taking a BTK inhibitor, NCCN experts recommend only taking 1 or 2 medicines that increase bleeding risk at the same time. It may be okay to take a BTK inhibitor and either aspirin or an anticoagulant. But taking a BTK inhibitor; an antiplatelet drug, such as aspirin; and an anticoagulant is risky.

If you need surgery, your oncologist will pause treatment with the BTK inhibitor to prevent major bleeding. The BTK inhibitor is put on hold for 3 days before and after minor surgery. For major surgery, treatment is paused for 7 days before and after surgery.

Will I need blood transfusions?

Some people being treated for CLL need a blood transfusion. The transfusion should be done according to hospital standards. All blood should be treated with radiation before the transfusion. This will prevent the rare event of transfused blood attacking your body.

Where can I go to learn more about supportive care?

The full library of NCCN Guidelines for Patients has several guides on supportive care. These guides focus on the treatment of common physical and emotional effects of many cancers. The library of NCCN Guidelines for Patients is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

These are some of the supportive care guides that are available:

Distress During Cancer Care

Everyone with cancer feels distress at some point. It's normal to be worried, sad, helpless, or angry.

Fatigue and Cancer

Cancer-related fatigue (tiredness) is not the typical tiredness that follows an active or long day. It's a distressing lack of energy that does not improve with regular rest or sleep, and it disrupts life.

Palliative Care

Palliative care is an approach to health care for people living with serious illnesses, including cancer. It focuses on providing relief from the symptoms and stress of having cancer.

The full library of NCCN Guidelines for Patients has several guides on supportive care at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Nausea and Vomiting

Cancer treatments can sometimes cause nausea and vomiting. Nausea is the feeling that you are going to throw up. Vomiting is forcefully throwing up what's in your stomach. Treatments are available to help with both complications.

Low Blood Cell Counts

Certain cancer treatments can cause a drop in red or white blood cells. When there are low levels of a type of white blood cell called neutrophils, it's called neutropenia. You're more likely to get infections when white blood cell counts are low. A low number of red blood cells, called anemia, may cause fatigue.

Graft-Versus-Host Disease

A possible side effect of a hematopoietic cell transplant is graft-versus-host disease. This side effect occurs when donor cells attack your healthy cells.

Immunotherapy Side Effects: Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are used to treat some types of Richter's transformation. Immune-related side effects can occur during or after treatment. Your care team will watch for certain side effects if you are being treated with an immune checkpoint inhibitor.

Immunotherapy Side Effects: CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy can cause serious side effects, including nervous system dysfunction. If you're having CAR T-cell treatment, review the *NCCN Guidelines for Patients: Immunotherapy Side Effects CAR T-Cell Therapy*.

Survivorship Care for Cancer-Related Late and Long-Term Effects

Cancer and its treatment can cause long-term and late side effects. Long-term effects begin during treatment and continue after treatment ends. Less often, side effects start long after treatment has ended. Late and long-term effects include fatigue, poor sleep, pain, and depression.

Survivorship Care for Healthy Living

People with cancer need to maintain a healthy lifestyle. Healthy living may help prevent disease and improve well-being. Topics covered in this guide include physical activity, food, tobacco use, and sun protection.

Key points

- Supportive care is cancer care that improves quality of life. It helps prevent life-threatening health conditions and provides symptom relief. It can also help with things like paying for care or getting transportation to the doctor.
- Supportive care for chronic lymphocytic leukemia (CLL) can also help with treating common side effects and can help keep you healthy.
- Common side effects that your care team may pay extra attention to are CLL-related infections, autoimmune cytopenias, tumor lysis syndrome, tumor flare, blood clots, and bleeding as well as bruising.
- People with CLL are at risk of getting infections. Protect yourself by getting vaccinations (but not live vaccines). Certain treatments for CLL can weaken the immune system. You may take medicines to prevent infections caused by weakened immunity.
- People with CLL are at risk for second cancers, so don't skip screenings for other cancers.
- Blood tests will be done often to check on the CLL.

Questions to ask

- Who can I talk to about help with housing, food, transportation, and other basic needs?
- How can I connect with others and build a support system?
- How much will I have to pay for my treatment? What help is available to pay for medicines and other treatments?
- Am I at risk for specific side effects?
- Who should I contact if I experience side effects?

I found focusing and staying in touch with a small circle of close friends who really care about me helped build my mental strength. It will be easy to identify them, and the good feeling you have after a text or chat is great mental strength fuel."

7

If CLL changes into another cancer: Richter's transformation

In a few people, chronic lymphocytic leukemia (CLL) changes into a different, aggressive cancer. This change is called Richter's transformation or Richter's syndrome. It can occur before or after CLL treatment.

In uncommon cases, chronic lymphocytic leukemia (CLL) can quickly transform into a more serious cancer. Most often, it transforms into diffuse large B-cell lymphoma (DLBCL). Less often, it changes into Hodgkin lymphoma. In either case, this change is called Richter's transformation.

Richter's transformation can arise from specific mutations or genetic abnormalities in CLL cells.

Tests to diagnose Richter's transformation

Tests are needed to confirm if you have Richter's transformation and to plan treatment. These tests are like those for CLL described in *Chapter 2: Tests for CLL*.

Confirming transformed CLL

Lymph nodes that are suddenly swollen, fever when you don't have an infection, night sweats, and pain in the stomach area (caused by a swollen spleen) are symptoms of Richter's transformation. A biopsy is needed to diagnose Richter's transformation.

Imaging results from a whole-body FDG-PET/CT scan will be used to select the best area for biopsy. A PET/CT scan uses 2 imaging technologies at the same time:

- PET scans highlight cells that may be cancerous, and they can show even small amounts of cancer.
- CT scans use x-rays to take many images of your body from different angles.

After the imaging scan, an incisional biopsy (which removes part of the lymph node) or excisional biopsy (which removes the whole lymph node) will be done to examine your lymph nodes. Then, a hematopathologist will examine and test the lymph node samples. They'll look for signs of Richter's transformation.

If the results from the lymph node biopsy aren't clear, your bone marrow may be biopsied. For more information on a bone marrow biopsy and aspiration, see *Chapter 2: Tests for CLL*.

More tests for Richter's transformation

You will also have some of the same tests done that you had before when CLL was first diagnosed. This includes a physical exam and updated medical history. Performance status, B symptoms, a complete blood count with differential, a comprehensive metabolic panel, lactate dehydrogenase (LDH) levels, and uric acid levels will be checked, too.

A molecular analysis will also be done to understand how the cancer is changing. If needed, other tests might be done, too.

Your care team will check on you throughout this process. Let them know how you're feeling, and they can help. *Chapter 6: How supportive care can help you* describes supportive care that helps with treatment side effects, worried feelings, and more.

Additional tests that might be needed

In certain cases, more tests may be given. Because old viruses in your body can reactivate, testing for Epstein-Barr and hepatitis viruses could be useful. And depending on your treatment options, you might get a heart scan or a human leukocyte antigen (HLA) test. A scan of your heart is needed to decide if anthracyclines (a type of chemotherapy) are safe. An HLA test is required if you might receive a hematopoietic cell transplant (the test will help find a donor).

Additionally, some cancer treatments can hurt reproductive organs and harm unborn babies. You may receive a referral to a fertility specialist before starting cancer treatment. If needed, your care team will also check if you're pregnant.

How is Richter's transformation treated?

Treatment for Richter's transformation starts right after diagnosis with the goal of extending life. Treatment is based on the type of cancer CLL has transformed into (either DLBCL or Hodgkin lymphoma). **Guide 8** describes all of the treatments someone with Richter's transformation could receive if the CLL changed to DLBCL.

Drugs called immune checkpoint inhibitors and bispecific antibodies are options for Richter's transformation. Keep reading to learn more about when some of these therapies are given.

Diffuse large B-cell lymphoma

DLBCL tumors have fast-growing, large B cells. DLBCL is commonly found in lymph but can also be found in the spleen, liver, bone marrow, or other tissues and organs.

The recommended treatments depend on whether DLBCL evolved from CLL cells.

If DLBCL did not evolve from CLL cells, a clinical trial or chemoimmunotherapy regimens are the first options. Ask your care team if there is an open clinical trial that's a good fit for you. New treatments may be available through clinical trials.

If a clinical trial is not an option, rituximab-based chemoimmunotherapy is often used for treatment. Chimeric antigen receptor (CAR) T-cell therapy, immune checkpoint inhibitor-based regimens, BTK inhibitors, and bispecific antibody therapies may be options later on for this kind of Richter's transformation.

If DLBCL evolved from CLL cells, or if it's unknown how CLL evolved into DLBCL, a clinical trial or certain drug therapies are preferred. These therapies include BTK inhibitors, immune checkpoint inhibitors, and bispecific antibody therapies. The chemoimmunotherapy regimens are other recommended options in this case.

Guide 8
Treatments for Richter's transformation from CLL cells to DLBCL

Chemoimmunotherapy	DA-EPOCH-R: Dose-Adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin, plus Rituximab
	HyperCVAD: Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone, plus Rituximab alternating with Cytarabine and High-Dose Methotrexate
	OFAR: Oxaliplatin, Fludarabine, and Cytarabine, plus Rituximab
	RCHOP: Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone, plus Rituximab
BTK inhibitor	Pirtobrutinib
BTK inhibitor plus immune checkpoint inhibitor	Zanubrutinib plus Tislelizumab-jsgr
Immune checkpoint inhibitor-based therapy	Nivolumab with or without Ibrutinib
	Pembrolizumab with or without Ibrutinib
	Atezolizumab plus Venetoclax and Obinutuzumab
Bispecific antibody therapy	Epcoritamab-bysp
	Glofitamab-gxbm
CAR T-cell therapy (after at least 1 prior regimen with systemic therapy)	Axicabtagene Ciloleucel
	Lisocabtagene Maraleucel
	Tisagenlecleucel

Hodgkin lymphoma

In Hodgkin lymphoma, white blood cells called lymphocytes look abnormally large and may have more than 1 nucleus (the control center of the cell).

A clinical trial is the preferred treatment option for CLL that changed to Hodgkin lymphoma. Other treatments include those that are used to treat Hodgkin lymphoma, and the recommendations for treating this cancer are available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Key points

- Richter's transformation is a change from chronic lymphocytic leukemia (CLL) to an aggressive lymphoma. The diagnosis is confirmed with imaging and biopsies.
- Richter's transformation is treated based on whether the CLL changed to diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma.
- The treatment options for when CLL changes into DLBCL depend on how the CLL changed into DLBCL.
- If DLBCL did not evolve from CLL cells, a clinical trial or a chemoimmunotherapy regimen is the first option. If it did evolve from CLL or it's not clear how it evolved, a clinical trial or other drug therapies are recommended.
- The preferred treatment option for Richter's transformation to Hodgkin lymphoma is a clinical trial. Other recommended treatment options can be found in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hodgkin Lymphoma.

Questions to ask

- What treatment would be appropriate for me now that I have Richter's transformation?
- What are the symptoms of Richter's transformation?
- Do you follow NCCN Clinical Guidelines to treat DLBCL and Hodgkin lymphoma?

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

8
Other resources

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

What else to know

This patient 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 difference between CLL and SLL
- The possibility of Richter's transformation
- Watch and wait, and how long before they will receive treatment
- Their care team and how they will help during watch and wait and during treatment
- Getting financial help

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.

In addition to help from your providers, the resources listed in the next section provide support for many people like yourself.

Where to get help

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

AnCan Foundation
ancan.org

Bag It Cancer
bagitcancer.org

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

Blood Cancer United
bloodcancerunited.org

Cancer*Care*
cancercare.org

Cancer Hope Network
cancerhopenetwork.org

CLL Society
cllsociety.org

GRACE
cancergrace.org

HealthTree Foundation
healthtree.org

Imerman Angels
imermanangels.org

Leukemia Research Foundation
leukemiarf.org

Lymphoma Research Foundation
lymphoma.org

National Bone Marrow Transplant Link (nbmtLINK)
nbmtlink.org

NMDP
nmdp.org/one-on-one

PAN Foundation
panfoundation.org

Stupid Cancer
stupidcancer.org

TargetCancer Foundation
targetcancer.org

Triage Cancer
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?
- Are there other services available to me and my caregivers?
- How can I connect with others and build a support system?

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

anemia
A health condition in which a blood protein called hemoglobin is low.

antibody
A protein in blood that helps fight off infection. Also called an immunoglobulin.

B cell
A type of white blood cell called a lymphocyte. Also called a B lymphocyte.

beta-2 microglobulin
A small protein made by many types of cells.

biomarkers
Measurable characteristics and features that show what's happening in a cell or an organism. These can be used to plan treatment specifically for you.

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

bone marrow
The sponge-like tissue in the center of most bones where blood cells are made.

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.

B symptoms
A set of symptoms caused by some B-cell cancers.

bruton's tyrosine kinase (BTK) inhibitors
A type of targeted theapy. These drugs are oral medications that target the BTK protein.

cancer stage
A rating of the outlook of a cancer based on its growth and spread.

CAR T-cell therapy
A type of immunotherapy that re-engineers a person's T cells so that they can attack cancer cells.

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

chromosome
A structure within cells that packages DNA and coded instructions for cell behavior (genes).

chronic lymphocytic leukemia (CLL)
A type of blood cancer that grows slowly and affects lymphocytes (a type of white blood cell).

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

complete blood count (CBC) with differential
A lab test that measures the number of red blood cells, white blood cells, and platelets. A differential examines the number of each type of white blood cell.

comprehensive metabolic panel
Lab tests of up to 14 chemicals in your blood. Also called the comprehensive chemistry panel.

computed tomography (CT)
A test that uses x-rays from many angles to make a series of pictures of the inside of the body.

diagnosis
An identification of an illness based on tests.

diffuse large B-cell lymphoma (DLBCL)
A blood cancer that CLL can sometimes change into.

fatigue
Severe tiredness despite getting enough sleep that limits one's ability to function.

fertility counselor
An expert who helps people have babies.

flow cytometry
A lab test of substances on the surface of cells to identify the type of cells present.

fluorescence in situ hybridization (FISH)
A lab test that uses special dyes to look for abnormal chromosomes and genes.

gene
Coded instructions in cells for making new cells and controlling how cells behave.

hematologists
Doctors who are experts in blood diseases and cancers.

hematopathologist
A doctor who is trained to study blood diseases involving different organs.

hematopoietic cell transplant
A cancer treatment that replaces abnormal blood stem cells with healthy donor cells. Also called a stem cell or bone marrow transplant.

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

immune system
The body's natural defense against infection and disease.

immunoglobulin
A protein made by B cells to help fight off infection. Also called an antibody.

karyotype
A lab test that makes a map of chromosomes to find defects.

lactate dehydrogenase (LDH)
A protein in blood that helps to make energy in cells.

lymphatic system
A network of organs and vessels that collects and transports a fluid called lymph.

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

lymphocyte
One of the 3 main types of white blood cells that help protect the body from illness.

lymphoma
A cancer of white blood cells called lymphocytes that are within the lymphatic system.

lymph vessel
A small tube-shaped structure through which a fluid called lymph travels.

medical history
A report of all of your health events and medications.

next-generation sequencing (NGS)
A lab test used to detect abnormal changes in DNA.

pathologist
An expert who tests cells and tissues to find disease.

performance status
A rating of one's ability to do daily activities.

physical exam
A study of the body for signs of disease.

positron emission tomography (PET)
A test that uses radioactive material to see the shape and function of body parts.

prognosis
The likely course and outcome of a disease.

pure red cell aplasia
A health condition in which the number of young red blood cells is very low.

Richter's transformation
A change from a slow-growing leukemia into a fast-growing lymphoma. Also called Richter's syndrome.

side effect
An unhealthy or unpleasant physical or mental response to treatment.

small lymphocytic lymphoma (SLL)
The same cancer as CLL, but the difference between the two cancers is where the cancer cells are found. SLL is most commonly found in lymph nodes.

spleen
An organ to the left of the stomach that helps protect the body from disease.

staging system
A rating scale of the outlook of CLL.

supportive care
Health care that includes symptom relief but not cancer treatment. Also called palliative care.

tumor lysis syndrome
A health condition caused by the rapid death of many cancer cells.

uric acid
A chemical that is made when cells and certain eaten food break down.

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

NCCN.org/patients/comments

NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 1.2026. It was adapted, reviewed, and published with help from the following people:

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For contact information visit NCCN.org/cancercenters.

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Dana-Farber/Brigham and Women's Cancer Center |
Mass General Cancer Center
Boston, Massachusetts

Duke Cancer Institute
Durham, North Carolina

Fox Chase Cancer Center
Philadelphia, Pennsylvania

Fred & Pamela Buffett Cancer Center
Omaha, Nebraska

Fred Hutchinson Cancer Center
Seattle, Washington

Huntsman Cancer Institute at the University of Utah
Salt Lake City, Utah

Indiana University Melvin and Bren Simon
Comprehensive Cancer Center
Indianapolis, Indiana

Johns Hopkins Kimmel Cancer Center
Baltimore, Maryland

Mayo Clinic Comprehensive Cancer Center
Phoenix/Scottsdale, Arizona
Jacksonville, Florida
Rochester, Minnesota

Memorial Sloan Kettering Cancer Center
New York, New York

Moffitt Cancer Center
Tampa, Florida

O'Neal Comprehensive Cancer Center at UAB
Birmingham, Alabama

Robert H. Lurie Comprehensive Cancer Center
of Northwestern University
Chicago, Illinois

Roswell Park Comprehensive Cancer Center
Buffalo, New York

Siteman Cancer Center at Barnes-Jewish Hospital
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St. Louis, Missouri

St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center
Memphis, Tennessee

Stanford Cancer Institute
Stanford, California

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Columbus, Ohio

The UChicago Medicine Comprehensive Cancer Center
Chicago, Illinois

The University of Texas MD Anderson Cancer Center
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UC Davis Comprehensive Cancer Center
Sacramento, California

UC San Diego Moores Cancer Center
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UCLA Jonsson Comprehensive Cancer Center
Los Angeles, California

UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California

University of Colorado Cancer Center
Aurora, Colorado

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Ann Arbor, Michigan

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Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

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New Haven, Connecticut

Index

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Cancer care recommendations from leading experts at the
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Chronic Lymphocytic Leukemia

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PAT-N-1929-0426