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#Reference From NCCN Guidelines

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CLL basics

- 5 What is CLL?
- 6 Are CLL and SLL related?
- 7 What's the best treatment?
- 7 Key points

Chronic lymphocytic leukemia is a type of blood cancer. It is unlike many other cancers because it worsens slowly. Treatment may not be needed for years, and there are newer treatments that extend life for a long time.

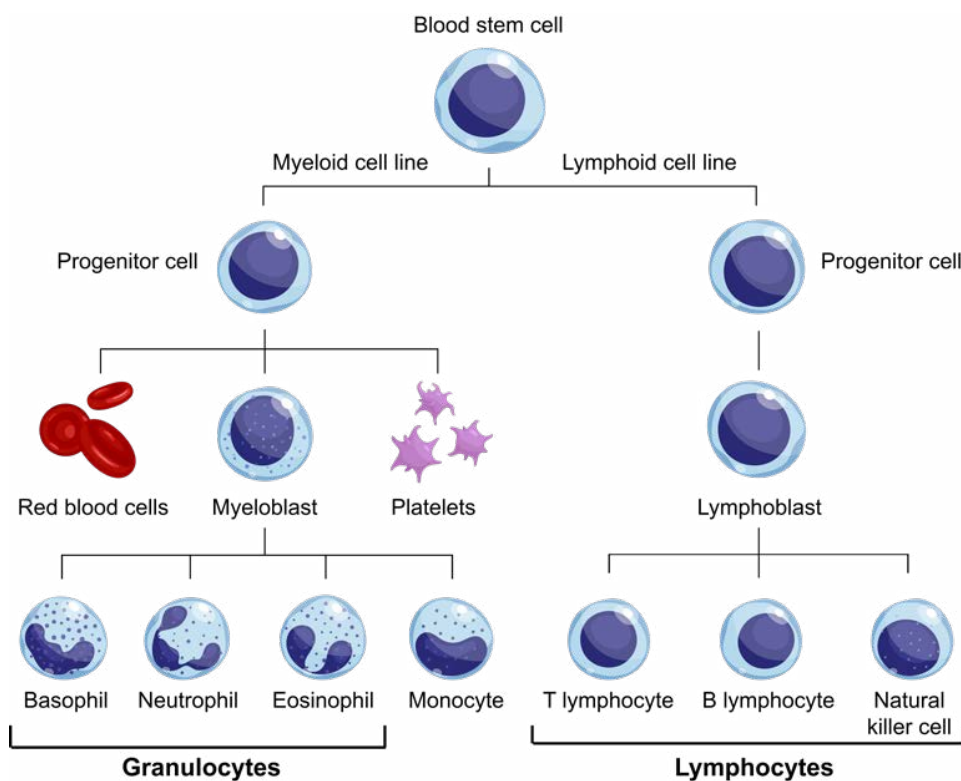
What is CLL?

Chronic lymphocytic leukemia (CLL) is cancer of B cells. Also called B lymphocytes, B cells are a type of white blood cell. White blood cells help fight harmful germs in the body.

Cancer is a disease that causes cells to grow out of control. Normal B cells increase in number when there is an infection. In contrast, CLL cells always increase in number. Tests can show if a rise in lymphocytes is caused by an infection or CLL.

B cells

Blood cells form in bone marrow then enter the bloodstream when they're mature. Mature white blood cells include monocytes, granulocyte, and lymphocytes. B cells (or B lymphocytes) help your body remember harmful germs that invade your body. They also make antibodies that attack germs.



In addition to uncontrolled growth, CLL cells don't function correctly. They may not fight infections as well as normal B cells. Some people with CLL take medicine to prevent infections.

Are CLL and SLL related?

CLL and small lymphocytic lymphoma (SLL) are the same cancer. They differ only by the location of the cancer cells.

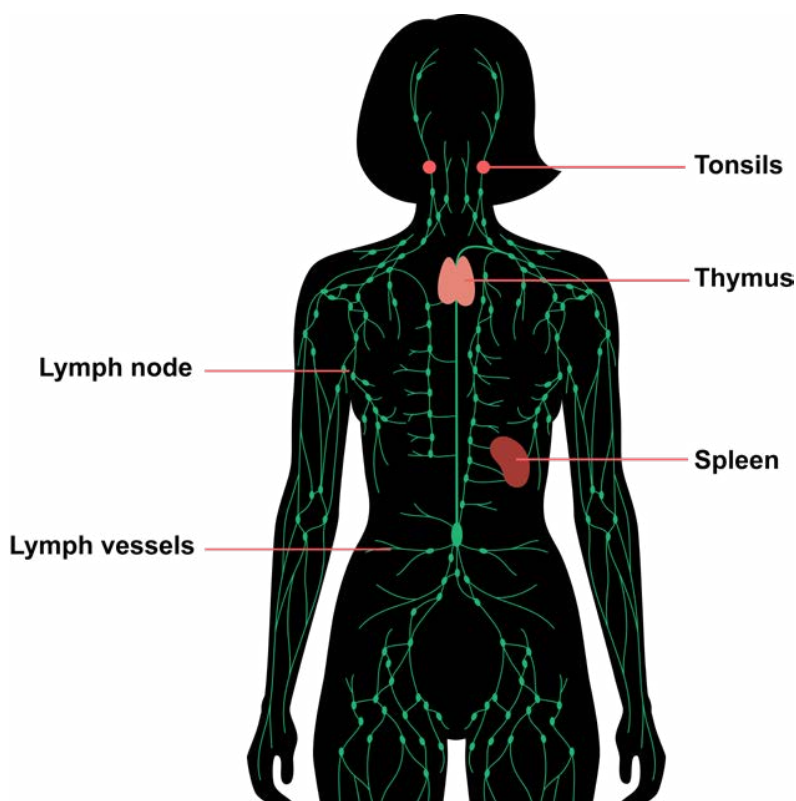
CLL cells are found in the blood and bone marrow but may also be in the lymph system. Lymph nodes and the spleen may be larger than normal because of a buildup of CLL cells.

There are few, if any, SLL cells in blood. Instead, SLL cells are mainly in lymph nodes and the spleen. SLL may be found because of painless, swollen lymph nodes.

Treatment of CLL and SLL is very similar because the cancer cells are the same.

Lymph system

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



What's the best treatment?

There's no treatment for CLL that's best for everyone. The best treatment is the treatment that's right for you. It's also important to know that many people don't need treatment right away, if ever.

This book explains how cancer care experts—oncologists—predict when treatment is helpful. It also explains tests and treatments for CLL. The recommendations in this book are based on the latest science and practices at top cancer centers.

Newer treatments for CLL work well for many people. Treatment reduces the number of CLL cells and raises numbers of normal blood cells. Treatment will also likely help you feel better and live longer. But it does not cure CLL. Many people receive a series of treatments that control CLL for a long time.

Most people with CLL live a fairly normal life, but usually, there are challenges. You'll need to cope with not knowing exactly when treatment will be needed. You might have to live with symptoms caused by CLL or treatment. You will need to take extra care to avoid infections. Supportive care can help you deal with these challenges.

You are a member of your cancer care team. You can take part in treatment planning. There is a list of suggested questions in Chapter 7 to ask your team. You're more likely to get the care you want by asking questions and making decisions with your team.

Key points

- CLL is a cancer of B cells that are found in high numbers in the bloodstream.
- SLL is the same cancer as CLL but mainly involves the lymph system.
- Many people with CLL can live years without starting treatment.
- Over years, several lines of treatment may be needed to keep CLL in check.
- Supportive care can help prevent or relieve problems caused by CLL.



I am very grateful I had a consultation with a CLL specialist. It was reassuring to finally speak to a CLL specialist. The doctor answered all my questions thoroughly. I am very satisfied with the advice I received."

2

Tests for CLL

- 9 Confirming CLL
- 11 Planning cancer care
- 14 Preserving fertility
- 14 Predicting the outlook
- 15 Key points

There are many types of B cell cancers, so it is important that certain tests are done to identify chronic lymphocytic leukemia. To plan cancer care, more tests will be done to decide when to start treatment, what treatment will likely work best, and what supportive care is needed.

Confirming CLL

The only way to be sure that you have cancer is to test samples from your body. Most often, chronic lymphocytic leukemia (CLL) is diagnosed by testing a blood sample.

The tests for diagnosis are done at a lab. A doctor called a hematopathologist is an expert at diagnosing cancers of blood and immune cells. They spend much of their time working with samples of blood, bone marrow, and lymph tissue.

Lab results used for diagnosis are included in a pathology report. This report will be sent to your hematologist/oncologist—an expert in blood cancers. You may be able to view the pathology report using an online patient portal, or ask for a copy. The report is used to plan your treatment. Your oncologist will review the results with you. Take notes and ask questions.

Diagnosis by blood tests

The hematopathologist will examine a drop of your blood using a microscope. This is called a blood smear. Your oncologist may also view the blood smear. The features of the abnormal cells can be a clue as to what cancer you have.

Your blood will also be tested using a method called flow cytometry. This test shows which cells are in the blood. It can detect common patterns of proteins on the surface of cells called the immunophenotype. The immunophenotype of CLL includes CD5, CD19, and CD23, some CD20, and no CD10 proteins.

Flow cytometry is also used for an absolute monoclonal B lymphocyte count. A CLL diagnosis requires at least 5,000 monoclonal B lymphocytes in blood.

Diagnosis by biopsy

A biopsy is a procedure that removes harder-to-reach samples from the body for testing. If the blood results aren't clear, a biopsy of lymph nodes is often done next to confirm CLL. Regardless of blood results, small lymphocytic lymphoma (SLL) should be confirmed by tests of lymph nodes.

An excisional biopsy removes a whole lymph node, and an incisional biopsy removes part of a lymph node. Needle biopsies can be done when the other biopsies are not safe. A lab method called immunohistochemistry (IHC) will be used to find the immunophenotype of the biopsied cells.

It is very rare that tests of bone marrow are needed for diagnosis. Bone marrow is the soft center in the middle of most bones. It is like a sponge holding liquid and cells.

A bone marrow biopsy removes a core sample of marrow. A bone marrow aspiration removes liquid and cells. These procedures are often done at the same time. They're performed on the back of the hip bone. You may receive an injected pain blocker or light sedative to relax you beforehand.

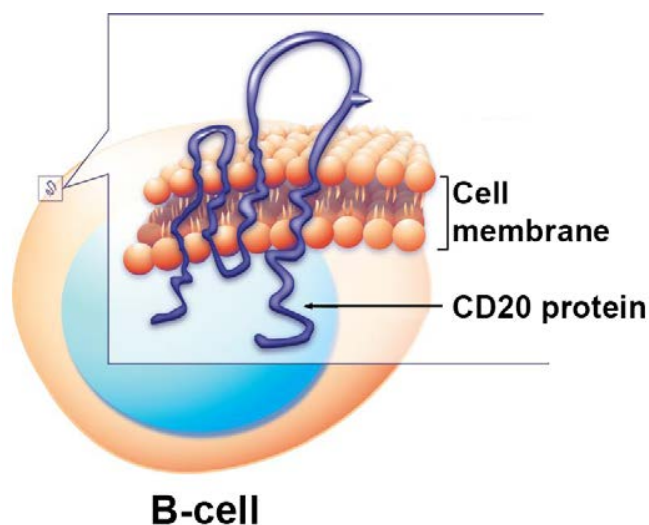


The key to managing fear is in making informed decisions. Stay positive, make a plan for yourself, and go forward one step at a time."

Immunophenotype

Chronic lymphocytic leukemia often has a common pattern of surface proteins on its cells. An example of these proteins is CD20 (shown). A common pattern of cell proteins is called an immunophenotype. It helps identify the correct type of cancer. For instance, CLL cells have proteins called CD200 and LEF1, but another type of lymphoma, called mantle cell lymphoma, does not have them.

Derivative work of NIAID - Rituxima Binding to CD20 on a B Cell Surface, CC BY 2.0, <https://commons.wikimedia.org/w/index.php?curid=39933221>



Planning cancer care

Your oncologist will consider many factors to plan the best care for you. The tests used to provide care are listed in **Guide 1** and are described next.

Health history

Expect your care team to review your health in detail. This is known as taking a medical history. They will want to know a lot about your past and current health. You will likely be asked about:

- Illnesses (especially infections) and injuries

- Prescribed and over-the-counter medicines and supplements, surgeries, and blood transfusions
- Lifestyle choices, including your diet, how active you are, and whether you smoke or drink alcohol
- Symptoms and complications of CLL

CLL can cause B symptoms, which are:

- Fevers when you don't have an infection,
- Drenching night sweats, and
- Unexplained weight loss.

Some cancers and other health problems can run in families. Be prepared to discuss

Guide 1

Tests used to plan treatment of CLL

Tests that are needed for planning

- Medical history including B symptoms and family history
- Physical exam including lymph nodes, spleen, and liver
- Performance status
- CBC with differential
- Comprehensive metabolic panel
- Beta-2 microglobulin
- FISH, DNA sequencing, and CpG-stimulated karyotype

Tests that may be useful for planning

- LDH
- Quantitative immunoglobulins
- Reticulocyte count, haptoglobin, and direct antiglobulin (Coombs) test
- Uric acid
- Hepatitis B and hepatitis C test
- Bone marrow biopsy and aspirate
- Diagnostic CT of chest, abdomen, and pelvis
- Pregnancy test

the health of your close blood relatives. These include brothers, sisters, parents, and grandparents. Relatives are 7 to 8 times more likely to develop CLL if there's a family history.

Physical exam

Your oncologist will perform a thorough physical exam of your body. This exam may include:

- Checking your vital signs—blood pressure, heart rate, breathing rate, and body temperature—and assessing your overall appearance
- Feeling and listening to organs
- Assessing 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 oncologist will look at and gently press on your body to assess their size. Areas that may be touched include your neck, armpit, belly, and groin.

Performance status

Performance status is your ability to do day-to-day activities. Your oncologist will rate your performance status based on your health history and exam.

Blood tests

Blood tests can measure blood cells, proteins, and chemicals in the bloodstream. If not done recently, a **complete blood count (CBC) with differential** is needed.

- A CBC measures parts of the blood including counts of white blood cells, red blood cells, and platelets.
- A differential measures the counts of the most common types of white blood cells—basophils, neutrophils, eosinophils, monocytes, and lymphocytes. It also checks if the cell counts are in balance with each other.

The white blood cell and lymphocyte counts are often high at diagnosis of CLL. Other blood counts may be low.

A comprehensive metabolic panel is a screening test for many diseases. It often includes tests for up to 14 chemicals in the blood. Abnormal levels may mean your kidneys and liver are not working as they should.

Beta-2 microglobulin is a small protein found on most cells. It is released by cells into the blood, especially by B-cells. High levels of beta-2 microglobulin suggest CLL is growing.

Sometimes, other blood tests are useful. Your oncologist may need tests to provide supportive care or to assess for a change in the cancer. See Chapter 5 for information on supportive care and Chapter 6 for Richter's transformation.

Other elements in the blood that may be measured are:

- **Lactate dehydrogenase (LDH)** to assess for rapid cell death that may be related to cancer or autoimmune hemolytic anemia
- **Quantitative immunoglobulins** to assess your risk of infections
- **Haptoglobin, reticulocytes, and Coombs tests** to assess for autoimmune hemolytic anemia
- **Uric acid** to assess the risk of tumor lysis syndrome from dying cancer cells
- **Hepatitis B antibodies and antigens** since the virus could reactivate during certain cancer treatments
- **Hepatitis C antibodies and antigens** since the virus could affect treatment results

Bone marrow tests

Tests on bone marrow are not often needed to diagnose CLL. However, they may be done to assess the cause of low blood counts.

Biomarker tests

There are unique features of CLL cells that are used to plan treatment specifically for you. These features are a type of biomarker. Biomarkers are found with lab tests using either a blood or bone marrow sample:

- **Fluorescence in situ hybridization (FISH)** can show missing parts of chromosomes and extra chromosomes. It detects a biomarker called 17p deletion.

- **DNA sequencing** is used to look for mutations in the *TP53* and *IGHV* genes.
- A **karyotype** can show defects in chromosomes. A complex karyotype is an important biomarker. It is defined as 3 or more unrelated defects in chromosomes that occur in more than one cell.

Biomarkers used to select treatment are discussed in Chapter 4.

Diagnostic CT

Computed tomography (CT) is like a plain x-ray but makes a more detailed image. A diagnostic CT shows body tissue even more clearly.

Diagnostic CT uses a higher dose of radiation than regular CT. It also uses a contrast agent. Some people can't have contrast due to certain health issues. Ask if contrast is safe for you.

Diagnostic CT of your chest, abdomen, and pelvis may be needed for 2 reasons. One reason is to look for big lymph nodes that may be causing symptoms. Another reason is to assess the extent of the cancer before starting a treatment called venetoclax.

CT scans are done in the radiology department. A radiologist will review your scans and send the results to your oncologist.

Pregnancy test

Some cancer treatments can harm an unborn baby. Your cancer care team will give you a pregnancy test before treatment if needed. Your treatment options will depend on the results.

Preserving fertility

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

Fertility is the ability to have a baby. Some cancer treatments can damage the body parts needed for fertility. Ask your care team if you are at risk for impaired fertility. It can happen to people of any gender.

You may receive a referral to a fertility specialist. A fertility specialist is an expert in helping people have babies. The fertility specialist 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 at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



Predicting the outlook

Prognosis is the likely course and outcome of a disease based on tests. The prognosis predicts how the cancer will turn out. Some people with CLL want to know the prognosis, but others don't. Tell your care team what information you do and do not want to know.

There are several prognostic biomarkers of CLL treated with chemoimmunotherapy. More

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.



research is needed to know how they predict the results of targeted therapy:

- Biomarkers that make CLL harder to treat are 11q deletions, 17p deletions, *TP53* mutation, unmutated *IGHV*, and a complex karyotype. (Note: 11q deletion is a favorable marker for treatment with BTK inhibitors)
- Biomarkers that predict average outcomes include trisomy 12 and having normal chromosomes.
- Biomarkers that predict better outcomes include 13q deletion, normal *TP53*, and mutated *IGHV*.

Beta-2 microglobulin is also a prognostic biomarker. High levels mean that CLL will likely be harder to treat. The International Prognostic Index (IPI) is a scoring system for prognosis. Its scores are based on beta-2 microglobulin and other factors.

Key points

- A diagnosis of CLL is most often made with blood tests.
- To plan treatment, your care team needs to know your health history and will examine your body. Blood tests will be done to learn if CLL is growing and affecting organs. If you can get pregnant, your care team will give you a pregnancy test.
- More blood tests may be done to provide supportive care for serious health problems caused by CLL. Some people need bone marrow tests or imaging.

- Ask your care team if you are at risk for impaired fertility. There are ways to have a healthy baby after cancer treatment.
- Your care team may plan care based on likely outcomes called the prognosis. Prognostic markers differ between cancer treatments.



We want your feedback!

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

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

3

Watch and wait

- 17 Waiting is safe
- 17 Wellness while you wait
- 18 Predicting the start of treatment
- 20 Reasons to start treatment
- 20 Key points

Chronic lymphocytic leukemia often does not need to be treated right away. Your care team will regularly assess the cancer and start treatment when needed. This approach is called watch and wait.

Waiting is safe

You may start treatment for chronic lymphocytic leukemia (CLL) months or years after diagnosis. Some people never start treatment.

Treatment may not be started right away because CLL is unlike many cancers. It often worsens very slowly.

Current research has shown that delaying treatment is safe for many people. Ongoing research is testing whether to delay or start newer treatments of CLL. Reasons to delay treatment include:

- Early treatment of CLL does not lengthen life
- Treatment may cause health problems called side effects, be inconvenient, and have out-of-pocket costs
- There may be better treatments in the future

Wellness while you wait

Watch and wait is a period of testing for changes in cancer status. It is also called observation, active surveillance, and watchful waiting. Some people call this period, “watch and worry,” but usually their worry subsides after they learn about the process.

During watch and wait, your care team will monitor your symptoms and blood counts. Watch and wait can go on for years.

During watch and wait, you can take care of your health in several ways:

- First, go to your health appointments. Do not skip or delay them.
- Second, find support. Watch and wait can cause worry or anxiety. Support groups or professional support may be helpful.
- Third, live a healthy lifestyle to improve your overall health.

See Chapter 5 for information to help you during watch and wait. This chapter explains recommendations for vaccines and care for cancer symptoms. It also describes other NCCN resources that can help improve the quality of your life.

Predicting the start of treatment

How long before treatment is started is often unknown. Except for Lugano stage 1 SLL, the cancer stage by itself doesn't determine starting treatment. But the cancer stage is a clue as to how soon treatment will be needed if at all.

Rai stages

The Rai staging system is commonly used for CLL. The Binet staging system is another staging system of CLL. The Rai and Binet systems are often used together.

The Rai system consists of 5 cancer stages ranging from stage 0 to stage 4. Often, the stages are written with Roman numerals—stages 0, I, II, III, and IV. The criteria for each stage are listed in **Guide 2**.

The 5 stages can be condensed into three 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. Treatment is typically started within weeks to a few months.

Guide 2 Criteria for Rai stages of CLL

	Rai 0	Rai 1	Rai 2	Rai 3	Rai 4
Many lymphocytes (lymphocytosis)	●	●	●	●	●
Enlarged lymph nodes (lymphadenopathy)		●	●	●	●
Enlarged spleen, liver, or both (organomegaly)			●	●	●
Low numbers of red blood cells (anemia)				●	●
Low numbers of platelets (thrombocytopenia)					●

● required criterion ● may occur

Lugano stages

The Lugano modification of the Ann Arbor Staging System is used to stage SLL. There are 5 stages. Like Rai stages, treatment is more likely to start soon for higher stages.

- Stage 1 lymphoma is in one group of lymph nodes or one place outside of the lymph system.
- Stage 2 lymphoma is in two or more groups of lymph nodes that are on the same side of the diaphragm. It may have grown from lymph nodes into nearby areas.
- Stage 2 bulky lymphoma has areas that measure 7.5 centimeters or larger.
- Stage 3 lymphoma is in lymph nodes above and below the diaphragm. Or it is in lymph nodes above the diaphragm and in the spleen.
- Stage 4 lymphoma has widely spread outside of the lymph system.

Don't wait to start treatment of Lugano stage 1 SLL

Lugano stage 1 SLL is treated right away. Stage 1 SLL is in only 1 lymph node region. Since the cancer is in one area, the treatment approach differs from the approach used for other stages of SLL.



I found focusing and staying in touch with a small circle of close friends who really care about you 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."

Reasons to start treatment

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 start treatment.

In general, oncologists recommend treatment when the effects of cancer become worse than the risks of treatment. At this point, treatment may make you feel better. A high white blood cell count by itself is not a reason to treat CLL. Reasons to start treatment are listed in **Guide 3**.

Key points

- CLL often worsens slowly, so treatment may not be needed for months or years. Early treatment of CLL does not lengthen life.
- Your care team will regularly check the status of CLL during watch and wait.
- During watch and wait, you can take care of your health by going to appointments, finding support, and living healthfully.
- Higher cancer stages are more likely to need treatment sooner than lower stages.
- Treatment is started based on your wishes and advanced signs and symptoms of CLL.

Guide 3

Reasons to start treatment

You can enroll in a clinical trial that's assessing if early treatment is helpful.

You have major symptoms of CLL, such as:

- Severe fatigue
- Drenching night sweats
- Unintended loss of at least 10 percent of your body weight within 6 months
- Fever without an infection

CLL is causing one or more of your organs to stop working properly.

Your spleen or lymph nodes are growing quickly, are large, or are causing discomfort.

CLL is causing the number of red blood cells to decrease.

CLL is causing the number of platelets to decrease.

Treatment with steroids is not stopping your body from killing your red blood cells or platelets. This is called steroid-refractory autoimmune cytopenia.

4

Treatment of CLL

- 22 About treatment
- 23 Tests before treatment
- 23 Chemotherapy and immunotherapy
- 24 BTK and BCL-2 inhibitors
- 27 Clinical trials
- 29 Checking treatment responses
- 31 After BTK and BCL-2 inhibitors
- 33 Key points

There have been several breakthroughs in the treatment of chronic lymphocytic leukemia. NCCN experts recommend newer targeted therapies for most people. Discuss the treatment options in this chapter with your care team. They will plan treatment specifically for you.

About treatment

A team of experts will provide cancer treatment and support you. Your team will be led by a hematologist/oncologist. This doctor is an expert in treating blood cancers. Other common team members include nurses, patient navigators, social workers, and specialists.

Chronic lymphocytic leukemia (CLL) is treated with cancer drugs. A regimen consists of one or more drugs. In this chapter, preferred regimens are noted. Preferred regimens work better, are safer, or cost less than other options.

People with CLL are often treated over their lifespan with a series of regimens. The first treatment given is referred to as first-line therapy. Second-line therapy is the second treatment and so on.

All treatments can cause unwanted health problems called side effects. Side effects

Treatment of Lugano stage 1 SLL

CLL and small lymphocytic lymphoma (SLL) are treated the same except for Lugano stage 1 SLL. Instead of drug treatment, stage 1 SLL is treated with radiation therapy.

Radiation therapy uses high-energy x-rays to treat SLL. The cancer cells either die or can't make more cancer cells.

A radiation oncologist is a doctor who is an expert in treating cancer with radiation. This doctor will lead a team that designs your treatment plan and provides treatment.

During radiation therapy, you will lie on a table during treatment. A large machine makes radiation beams shaped to the form of the tumor. The machine aims the highest radiation dose at the cancer. Nearby healthy tissue may receive some radiation in the process.

Side effects of radiation therapy are cumulative. This means they build up slowly and are worse at the end of treatment. Common effects are feeling fatigued and skin changes. Often, people describe skin changes as like a sunburn.

vary from person to person. Ask your care team for a list of possible side effects of your treatments. Also, tell your team about any new or worsening symptoms you have. There may be ways to help you feel better. Care for key side effects is explained in Chapter 5.

Tests before treatment

CLL may change during watch and wait. It may also change after treatment starts. Before each line of treatment, the cancer will be tested.

Biomarker tests

CLL differs between people. Differences in how CLL behaves are caused by abnormal changes in cancer cells called biomarkers. Because biomarkers differ between people, a treatment that helps one person might not help you. That's why it's important to have biomarker tests and get a treatment plan specific to you.

NCCN experts recommend testing of the following biomarkers before treatment:

- **A 17p deletion** is a missing part of chromosome 17 that contains the *TP53* gene.
- **TP53 mutation** is an abnormal change in the *TP53* gene. This test is done because the *TP53* gene may be mutated instead of missing.
- **IGHV mutation** is an abnormal change in the *IGHV* region genes. This biomarker does not change over time. Testing is only needed if not done before.
- **A complex karyotype** is 3 or more unrelated defects in chromosomes that occur in more than one cell.

Biopsy and imaging

NCCN experts recommend a biopsy and computed tomography (CT) scan if needed. Most people with CLL don't need them.

Chemotherapy and immunotherapy

It is sometimes useful to first treat CLL with chemoimmunotherapy or immunotherapy. But most people start with targeted therapy, which is discussed in the next section.

- **Chemotherapy** kills fast-growing cells like cancer.
- **Immunotherapy** enables your immune system to kill cancer.
- **Chemoimmunotherapy** combines chemotherapy and immunotherapy.

Chemoimmunotherapy and immunotherapy are given in cycles of treatment days followed by days of rest. Almost all of the drugs are given as a slow injection called an infusion.

Chemoimmunotherapy

Chemotherapy alone was once the standard treatment of CLL. Often, it didn't have great results. Experts now know that it doesn't work well for CLL with 17p deletion or *TP53* mutation. So chemotherapy is only an option for CLL without 17p deletion and *TP53* mutation.

First-line chemotherapy for CLL includes CD20 antibodies. CD20 antibodies are a type of immunotherapy. They include obinutuzumab (Gazyva) and rituximab (Rituxan).

The fludarabine, cyclophosphamide, and rituximab (FCR) regimen works well for CLL with *IGHV* mutations but can cause severe health problems. So FCR is only recommended for people who are under 65 years of age and fairly healthy.

Chemoimmunotherapy may be received when first-line targeted therapy isn't an option. It is also sometimes used if a rapid decrease in the amount of cancer is needed. In these cases, the options are bendamustine with a CD20 antibody or obinutuzumab with chlorambucil.

CD20 antibodies

Immunotherapy is sometimes used for first-line therapy for the same reasons as listed for chemoimmunotherapy. It is a treatment option for CLL with or without 17p deletion and *TP53* mutation. One treatment option is obinutuzumab. Another option is high-dose methylprednisolone (HDMP) with a CD20 antibody.

Next steps

To learn about results, read on page 29 *Checking treatment responses*. If CLL grows, targeted therapy is recommended next.

BTK and BCL-2 inhibitors

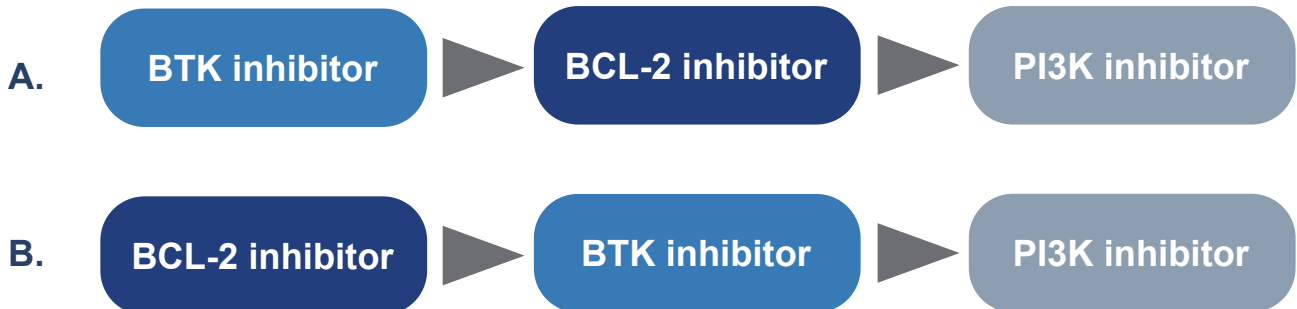
For many people with CLL, the first treatment is targeted therapy. Targeted therapy works by stopping the way in which CLL cells grow and survive.

- **BTK inhibitors** target a protein called Bruton's tyrosine kinase (BTK) that is inside of B cells. CLL is a cancer of B cells. BTK helps send a signal that tells the cells to grow. BTK inhibitors block BTK and stop the cells from growing.
- **BCL-2 inhibitors** target a protein called BCL-2 that is inside of B cells. In CLL, BCL-2 may build up and stop the cancer cells from dying. BCL-2 inhibitors allow the cancer cells to self-destruct.

Your oncologist will choose a regimen based on several factors. Biomarker testing is important. A complex karyotype may limit how

Treatment pathways

There are many treatment options for CLL, but some are more commonly used than others. Treatment for many people starts with either a BTK or BCL-2 inhibitor (shown below). In time, most people will need a different treatment. Often, treatment is switched from a BTK inhibitor to a BCL-2 inhibitor or the other way around. If you need a third type of treatment after taking BTK and BCL-2 inhibitors, there are also many options. One of these options is a PI3K inhibitor.



well BTK inhibitors work. Your age, overall health, and medications are other important factors.

First-line therapy

BTK inhibitors are taken for as long as they are working. They are pills taken at home. An CD20 antibody may be part of the regimen.

See Guide 4 for a list of regimens for first-line therapy.

Before starting a BTK inhibitor, your oncologist may assess your risk for diseases that affect the heart or blood vessels. This group of diseases is called cardiovascular or heart disease.

One treatment option is acalabrutinib (Calquence). Obinutuzumab is sometimes added to the regimen. Acalabrutinib is a preferred option as is zanubrutinib (Brukinsa). Zanubrutinib is used by itself to treat CLL.

Guide 4 First-line regimens for CLL

	CLL <i>without</i> 17p deletion and <i>TP53</i> mutation	CLL <i>with</i> 17p deletion or <i>TP53</i> mutation
BTK inhibitors		
Acalabrutinib with or without obinutuzumab	●	●
Zanubrutinib	●	●
Ibrutinib	●	●
Ibrutinib and obinutuzumab	●	
Ibrutinib and rituximab	●	
BCL-2 inhibitors		
Venetoclax with obinutuzumab	●	●
BTK and BCL-2 inhibitors		
Ibrutinib and venetoclax	●	●
Chemoimmunotherapy or immunotherapy		
FCR	●	
Bendamustine and either rituximab or obinutuzumab	●	
Obinutuzumab with chlorambucil	●	
Obinutuzumab	●	●
HDMP with either rituximab or obinutuzumab	●	●

- Preferred regimen because it works better, is safer, or costs less than other options or there is better research supporting its use

Ibrutinib often has very good results but is not a preferred option. It appears to cause more serious side effects, including heart disease, than other BTK inhibitors. A CD20 antibody may be used with ibrutinib, but more research is needed on these regimens.

Venetoclax (Venclexta) is the only BCL-2 inhibitor used to treat CLL. It is a pill taken at home. First-line venetoclax is taken with obinutuzumab.

Some people with CLL may prefer venetoclax over BTK inhibitors. First-line venetoclax is taken for 1 year and reduces CLL to very low levels. Taking venetoclax for a fixed time may prevent CLL from becoming unresponsive (resistant) to it.

Some research has been done on treatment with both **ibrutinib and venetoclax**. This regimen starts with taking only ibrutinib then adds venetoclax. It is taken for a limited time.

Second- and third-line therapy

The next treatment is based on results of prior treatments. **See Guide 5** for a list of regimens for second- and third-line therapy.

If CLL grows, the type of treatment is often switched. You may switch to a BTK inhibitor after a BCL-2 inhibitor or the other way around. The combined ibrutinib and venetoclax regimen may be another option.

Guide 5

Second- and third-line regimens for CLL

	CLL without 17p deletion and TP53 mutation	CLL with 17p deletion or TP53 mutation
BTK inhibitors		
Acalabrutinib	●	●
Zanubrutinib	●	●
Ibrutinib	●	●
Pirtobrutinib after taking other BTK inhibitors	●	●
BCL-2 inhibitors		
Venetoclax and rituximab	●	●
Venetoclax	●	●
Venetoclax with or without rituximab or obinutuzumab (preferred) if cancer relapses after prior venetoclax	●	●
BTK and BCL-2 inhibitors		
Ibrutinib and venetoclax	●	●

- Preferred regimen because it works better, is safer, or costs less than other options or there is better research supporting its use

There is a third option if CLL grows after venetoclax treatment is finished. This growth is called a relapse, and CLL may be treated with venetoclax again. Venetoclax may be taken with a CD20 antibody for a limited time. Obinutuzumab is the preferred CD20 antibody. Venetoclax may also be used by itself for as long as it controls cancer growth.

If treatment causes severe side effects, the type of treatment is often switched. If you're taking a BTK inhibitor, a second option is to take a different BTK inhibitor. A different inhibitor—acalabrutinib, zanubrutinib, or ibrutinib—may have less severe effects.

In the second- and third-line setting, pirtobrutinib is sometimes useful. It is a BTK inhibitor but works differently than the ones listed above. It is an option after treatment with one or more of the other BTK inhibitors.

Clinical trials

A clinical trial may be an option for treatment. It is a type of medical research study. After being developed and tested in a laboratory, 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 care team about whether a clinical trial may make sense for you.

Phases

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

- **Phase 1 trials** study the dose, safety, and side effects of an investigational drug or treatment approach. They also look for early signs that the drug or approach is helpful.
- **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 long-term safety and benefit of an FDA-approved treatment.

Who can enroll?

Every clinical trial has rules for joining, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. These requirements 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 group of experts called a research team. The research team 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 family,

friends, or others you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

Start the conversation

Don't wait for your team to bring up clinical trials. Start the conversation and learn about all of your treatment options. If you find a study that you may be eligible for, ask your team if you meet the requirements. If you have already started standard treatment, you may not be eligible for certain clinical trials. Try not to be discouraged if you cannot join. New clinical trials are always becoming available.

Frequently asked questions

There are many myths and misconceptions surrounding clinical trials. The possible benefits and risks are not well understood by many with cancer.

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 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. You may, however, have costs indirectly related to the trial, such as the cost of transportation or child care due to extra appointments. During the trial, you will continue to receive standard cancer care. This care is billed to—and often covered by—



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

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)

insurance. You are responsible for copays and any costs for this care that are not covered by your insurance.

Checking treatment responses

You will need to have tests to assess the treatment response. These tests include an updated medical history and physical exam, bloodwork, and sometimes imaging.

Types of responses

Based on tests, the response of treatment may be one of following:

- **Complete remission** is the best result. With a complete remission, enlarged organs and lymph nodes are back to normal size. You have no cancer symptoms like fever. Blood counts are within normal range. No CLL cells are detected in the bone marrow with common tests.
- **Partial remission** is a good result. Enlarged organs and nodes have shrunk to less than half their size. Blood counts have improved but are not normal.
- **Stable disease** is less than a partial remission. CLL is not growing.
- **Progressive disease** is growth of CLL.

CLL not in remission

The next steps of treatment depend on the type of outcome. Your treatment plan may not change if CLL is stable. 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 mutations

If you're on a BTK inhibitor, CLL may not be in remission because of *BTK* and *PLCG2* mutations. If tests find a mutation, you may switch treatment if the cancer is growing. If the cancer is stable, you can keep taking the same BTK inhibitor because it may control cancer growth for a couple of years.

Testing for transformed CLL

If CLL is growing while on any type of treatment, it may have transformed. CLL can change into a faster-growing cancer, which is described in Chapter 6. This doesn't happen often. Transformed CLL is confirmed by lab tests on a biopsy sample.

CLL in remission

After remission is achieved, your doctor will monitor the status of CLL. You will have regular visits with your care team. At visits, your medical history will be updated. You will have a physical exam and bloodwork.

Testing for minimal residual disease

When CLL is in complete remission, your oncologist may want to test for minimal residual disease (MRD). There could still be tiny amounts of cancer cells in blood when no cancer cells are seen with a microscope. This tiny amount of cancer is called MRD.

Lab tests used to detect MRD include:

- Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR)
- Six-color flow cytometry (MRD flow)
- Next-generation DNA sequencing (NGS)-based assays

A finding of undetectable MRD means the test detected no CLL cells. There may be no CLL cells or too few to be found. Despite these great results, CLL may not be cured.

Undetectable MRD is being studied as a predictor of outcomes. It may predict outcomes of time-limited treatment better than a complete remission. For now, it is not used to make treatment decisions.

Relapse

CLL tends to worsen over time, but it may take years before the next treatment is needed. Progressive disease after at least 6 months of remission is called a relapse. Larger lymph nodes or a larger liver or spleen are signs of a relapse. So is a large increase in the number of white blood cells called lymphocytes.

BTK inhibitors are taken until there is a relapse. At that time, a different treatment will be started quickly.

Chemoimmunotherapy and immunotherapy are received for a limited time. For most people, venetoclax is also taken for a fixed time. At relapse, treatment is started when there are signs that it is needed. These signs are explained in Chapter 3.



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 (and received) proper answers to all my questions."

After BTK and BCL-2 inhibitors

There are several treatment options after taking BTK and BCL-2 inhibitors. The first option explained below is clinical trials. Because of clinical trials, new treatments, such as pirtobrutinib, are now available to everyone.

A second option that your oncologist will consider is an allogeneic stem cell transplant. Most people with CLL do not get a transplant. You must not have major health problems other than cancer.

A third option is a recommended drug regimen. Many recommended regimens treat CLL in a different way than prior treatment.

Clinical trial

Experts are researching ways to better treat CLL after BTK and BCL-2 inhibitors. Ask your care team if there is a clinical trial that is a good fit for you. A clinical trial may provide access to a new way of stopping CLL that isn't available otherwise.

Allogeneic hematopoietic cell transplant

An allogeneic hematopoietic cell transplant uses donor cells to form healthy bone marrow in you. Hematopoietic stem cells are collected from a close relative or a stranger. These cells are in bone marrow and develop into every type of blood cell.

It may take some time to get the transplant. While you wait, you may get other treatment to reduce spleen size and improve symptoms.

There are several steps to receiving a transplant:

Step 1: Your blood will be tested for cell proteins called human leukocyte antigens (HLAs). A donor's HLA type must be a near-perfect match to yours for a transplant to work. Even with a near-perfect match, donor cells may attack your body. This is called graft-versus-host disease (GVHD).

Step 2: You'll receive treatment called conditioning to kill your bone marrow cells. Conditioning creates room for the donor cells. It also weakens the immune system so your body does not kill the donor cells.

Step 3: Next, you'll receive the donor cells through a transfusion. A transfusion is a slow injection of blood products into a vein. New, healthy blood cells will form over the next 2 to 4 weeks. This is called engraftment.

Step 4: You'll have to be extra careful to avoid germs for the first few weeks after the transplant. That's because your infection-fighting immune system will be almost gone. You may be given antibiotics to prevent or treat infection. You may receive medicine called immunosuppressants to prevent GVHD.

Recommended regimens

After treatment with BTK and BCL-2 inhibitors, there are a few new regimens for CLL. Also, some regimens that were options earlier in treatment are options now, too. **See Guide 6** on the next page for a complete list.

PI3K is a protein in the same chemical pathway that tells the cell to grow as is BTK. PI3K inhibitors block PI3K and cause the cells

4 Treatment of CLL » After BTK and BCL-2 inhibitors

to die. Duvelisib (Copiktra) is used by itself to treat CLL. Idelalisib (Zydelig) is used with or without rituximab.

Alemtuzumab (Campath) is a CD52 antibody—a type of immunotherapy—used to treat CLL. It marks the cancer cells so that the immune system can find and destroy the cells. Alemtuzumab may be received with or without the CD20 antibody rituximab.

Lenalidomide (Revlimid) is an immunomodulatory drug for CLL. It affects the immune system in multiple ways. It is used by itself or with rituximab to treat CLL.

Pirtobrutinib is a newer BTK inhibitor. It may be an option after taking the older BTK inhibitors if you haven't had it before.

Research on combining BTK and BCL-2 inhibitors is ongoing. Promising results have been found for when ibrutinib and venetoclax are used together.

Chemoimmunotherapy is an option only for CLL without 17p deletion and TP53 mutation. FCR is an option for people who are under 65 years of age and fairly healthy. Another recommended regimen is bendamustine with rituximab.

Immunotherapy can also be used after BTK and BCL-2 inhibitors. One option is obinutuzumab. Another option is HDMP with an CD20 antibody.

Guide 6 Regimens after BTK and BCL-2 inhibitors

	CLL <i>without</i> 17p deletion and TP53 mutation	CLL <i>with</i> 17p deletion or TP53 mutation
Duvelisib	●	●
Idelalisib with or without rituximab	●	●
Pirtobrutinib if not received before	●	●
Ibrutinib and venetoclax	●	●
Alemtuzumab with or without rituximab		●
FCR	●	
Lenalidomide with or without rituximab	●	●
Obinutuzumab	●	
Bendamustine and rituximab	●	
HDMP with either rituximab or obinutuzumab		●

Key points

- Tests of biomarkers that affect options are needed before starting treatment. New biomarkers may appear during watch and wait or after first-line therapy.
- A clinical trial tests new ways of stopping cancer in people. Ask your care team if there are clinical trials that are a good fit for you.
- The first treatment for CLL is often either a BTK or BCL-2 inhibitor. These treatments control cancer growth well.
- If the cancer grows or there are severe side effects, the type of treatment is often switched. You may switch to a BTK inhibitor after a BCL-2 inhibitor or the other way around.
- After treatment with BTK and BCL-2 inhibitors, you may have the option of a clinical trial. Other options are a hematopoietic cell transplant and a recommended drug regimen.



Let us know what you think!

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

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

5

Supportive care

35	About supportive care	38	Tumor flare
35	Vaccines for common infections	38	Blood clots
36	CLL-related infections	39	Bleeding
37	Second cancers	39	Blood transfusion
37	Autoimmune cytopenia	39	Supportive care guidelines
38	Tumor lysis syndrome	41	Key points

The goal of supportive care is to maintain or improve your quality of life. One of its aims is to prevent or relieve health problems caused by chronic lymphocytic leukemia or its treatment.

About supportive care

Supportive care is a key part of treatment for everyone with chronic lymphocytic leukemia (CLL). It is not just for people at the end of life who need hospice.

Supportive care is sometimes called palliative care since symptom relief is a main goal. But supportive care addresses many other needs. You can get help with food, financial aid, or family counseling.

Tell your care team about your symptoms and other needs to get the best supportive care. A palliative care specialist may be a member of your cancer care team. This specialist has received specific training to provide additional support to you. Some cancer centers have palliative care programs.

This chapter describes some of the unique needs of people with CLL. People with CLL are more likely to get infections, second cancers, and other health problems than other people. This chapter also lists NCCN resources on supportive care.

Vaccines for common infections

You can protect yourself by being up-to-date on your vaccines. Vaccines help prevent infections by training your body to quickly recognize and attack germs. They contain whole germs, parts of the germ, or a product of a germ, so your body can defend itself against future exposure.

Avoid live vaccines

People with CLL should avoid getting live vaccines unless approved by their oncologist. Live vaccines contain an entire germ that has been weakened (attenuated). They create a strong immune response to the real germ. Live vaccines may cause major health problems in people with weak immune systems.

Get recommended vaccines

Some vaccines are routine, and others are based on age, health, and other factors. Talk to your care team about which vaccines you need. NCCN experts recommend the following for people with CLL:

- The flu shot (influenza vaccine) every year but only a non-live type (inactive or recombinant)
- Pneumococcal vaccine as recommended by the U.S. Centers for Disease Control and Prevention
- Non-live (recombinant, adjuvanted) zoster vaccine to prevent shingles if you're on a BTK inhibitor
- COVID-19 vaccine

COVID-19

More research is needed to learn how well the COVID-19 vaccine works among people with CLL. The vaccine may not fully protect you, but there are additional ways to protect yourself. You can wear a mask. Keep a safe distance from others. And thoroughly wash your hands often.

If you get COVID-19, there are treatments for it. While being treated for COVID-19, your oncologist might pause your cancer treatment. Some COVID-19 treatments, like nirmatrelvir/ritonavir (Paxlovid), can interact with BTK inhibitors and venetoclax.

CLL-related infections

Normally, there are germs in the body that are harmless. But these germs can cause serious infections when cancer treatments weaken the body's immune system. Weakened immunity can also cause normal infections to be more

severe. These unusual and severe infections are called opportunistic infections.

Preventing infections

Medicine used to treat infections can also be used for prevention. Preventive care is based on the type of treatment for CLL. Some cancer treatments weaken the immune system more than others.

Herpes and fungal pneumonia

Acyclovir is an antiviral drug used to prevent infections caused by herpes viruses. These viruses include the herpes simplex virus and the varicella zoster virus. The varicella zoster virus causes chickenpox, and when reactivated, shingles.

Trimethoprim-sulfamethoxazole is a combined drug used to prevent pneumocystis jirovecii pneumonia. Pneumocystis jirovecii pneumonia is a lung infection caused by a common fungus.

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



Preventive care for herpes and fungal pneumonia is recommended during and after treatment with PI3K inhibitors, chemoimmunotherapy with fludarabine or bendamustine, and alemtuzumab. If you're on a BTK inhibitor, your oncologist will provide preventive care if needed and monitor for infection.

Neutropenia-related infections

While taking venetoclax, levels of white blood cells called neutrophils can drop. When levels are low (neutropenia), you are more likely to get infections. You'll need regular bloodwork during treatment. The antibiotic fluoroquinolone and antifungals help prevent infections caused by venetoclax-induced neutropenia.

Hepatitis

If you've had hepatitis B, it may be reactivated during cancer treatment. Entecavir is the medicine that is preferred for prevention and treatment. Other options are adefovir, telbivudine, and tenofovir. Preventive care may continue for up to 12 months after cancer treatment ends.

There is a link between hepatitis C and B-cell non-Hodgkin lymphomas. Direct-acting antiviral agents safely treat hepatitis C and may reduce lymphoma cells.

Cytomegalovirus

There is a high risk of cytomegalovirus reactivation when taking a PI3K inhibitor or alemtuzumab. Screening for reactivation should be done at least every 4 weeks. Reactivation may be prevented with the antiviral ganciclovir.

Treating ear, sinus, and lung infections

Some people with CLL get frequent, serious infections in their ear, sinuses, and lungs. Your oncologist will prescribe an antimicrobial, such as an antibiotic.

If your body isn't making enough immunoglobulin, you may take purified, donated immunoglobulin in addition to an antimicrobial. Intravenous immunoglobulin is received every month, or you can get injections under the skin every week.

Second cancers

People with CLL are at higher risk for other cancers, so regular cancer screening is important. There are screening programs for prostate, breast, cervical, lung, and colorectal cancers.

People with CLL are also at risk for melanoma and other skin cancers. Your risk is further increased if you can't tan, sunburn easily, or had major sun exposure as a child. See a dermatologist once a year for a skin exam.

Autoimmune cytopenia

Autoimmune cytopenia is a condition in which your immune system attacks your blood cells. There are several types. The most common types among people with CLL are autoimmune hemolytic anemia, immune-mediated thrombocytopenia, and pure red blood cell aplasia.

There are multiple treatment options for autoimmune cytopenia. Drug treatments include corticosteroids, rituximab, intravenous immunoglobulin, cyclosporin A, eltrombopag, and romiplostim. If steroids don't work or the cytopenia returns, BTK inhibitors may be used for treatment.

For some cytopenias, surgery may be an option. The spleen plays a key role in destroying platelets. Removing the spleen, called a splenectomy, can help restore the number of platelets.

Tumor lysis syndrome

Several treatments for CLL kill many cells quickly, such as:

- Chemoimmunotherapy
- Venetoclax
- Lenalidomide
- Obinutuzumab

Tumor lysis syndrome occurs when the waste released by dead cells is not quickly cleared out of the body. This may result in kidney damage and severe blood electrolyte disturbances. It can be life threatening.

Tumor lysis syndrome may be prevented with hydration. Drink lots of water. You may also get fluid infused into your bloodstream.

Medicines that lower uric acid can help, too. These medicines include allopurinol, febuxostat, or rasburicase. Some people are admitted to the hospital before starting treatment.

Tumor flare

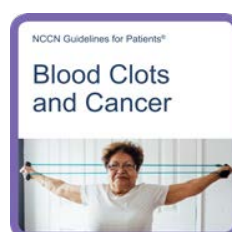
Lenalidomide may also cause tumor flare. Tumor flare is a fast, short-lived increase in cancer growth. Symptoms of tumor flare include enlarged lymph nodes or spleen, low fever, and rash.

Steroids are used for prevention and treatment of tumor flare. Preventive care is typically started if lymph nodes are big. The skin rash and itchiness caused by the flare can be treated with antihistamines.

Blood clots

Lenalidomide may cause blood clots. A blood clot is a clump of blood that may block blood vessels. Clots can be dangerous. If you're not taking an anticoagulant, clots can be prevented with aspirin while on lenalidomide. Aspirin is not needed if you are taking an anticoagulant.

If not taking lenalidomide, your chance for blood clots may still be high. More information on blood clots and cancer is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



Bleeding

BTK inhibitors increase the risk of bleeding and bruising. Your oncologist will monitor your bleeding risk based on all factors. Regular bloodwork is very important since bleeding risk increases when platelets are low (called thrombocytopenia).

When taking a BTK inhibitor, NCCN experts recommend taking only 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 anticoagulant. But taking a BTK inhibitor, antiplatelet, and an anticoagulant is risky.

If you will need surgery, your oncologist may pause the BTK inhibitor to prevent major bleeding. The 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.

Blood transfusion

Some people being treated for CLL will 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.

Supportive care guidelines

The library of NCCN Guidelines for Patients has several books on supportive care. These books focus on the treatment of common physical and emotional effects of many cancers. One book is about healthy living.

The library of NCCN Guidelines for Patients is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.

Distress

Everyone with cancer feels distress at some point. It is normal to be worried, sad, helpless, or angry. Distress can become severe and affect the way you live.

Fatigue

Cancer-related fatigue is not the typical tiredness that follows an active or long day. It is a lack of energy that is distressing, does not improve with normal resting or sleep, and 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.

Nausea and vomiting

Both chemotherapy and radiation therapy can 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.

Anemia and neutropenia

Chemotherapy often causes a drop in red and white blood cells. You are more likely to get infections when white blood cells counts are low (neutropenia). A low number of red blood cells (anemia) may cause fatigue.

Graft-Versus-Host Disease

A side effect of allogeneic hematopoietic cell transplants is graft-versus-host disease. This side effect is caused by donor cells attacking your healthy cells.

Immunotherapy side effects

Immune checkpoint inhibitors are used to treat some types of Richter's transformation. This treatment may cause your immune cells to attack your healthy cells. Immune-related side effects can occur during or after treatment.

Late and long-term effects

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

Healthy living

It's important to start or keep a healthy lifestyle. Healthy living may help prevent disease and improve well-being. Topics covered in the NCCN book 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.
- People with CLL are at risk for infections. Protect yourself by getting vaccinations, but avoid attenuated vaccines because they have live germs.
- Certain treatments of CLL can weaken the immune system. You may take medicines to prevent infections caused by weakened immunity. If you get frequent, severe infections, immunoglobulin may be added to the treatment of infections.
- People with CLL are at risk for second cancers. Don't skip cancer screenings.
- Advanced CLL and some CLL treatments may cause your immune system to attack your blood cells. This is called autoimmune cytopenia. There are multiple treatment options including steroids.
- Several treatments of CLL may cause tumor lysis syndrome. Hydration helps prevent this syndrome by removing dead cells from the body. Uric acid reducers may help, too.
- There may be a rapid increase in cancer growth right after starting lenalidomide. This is called a tumor flare and is treated with steroids. Lenalidomide may also cause blood clots. Aspirin or an anticoagulant helps prevent clots.

- The library of NCCN Guidelines for Patients includes books on supportive care. These books focus on common effects of cancer and its treatment, such as distress, nausea and vomiting, poor sleep, and fatigue.



I'm newly diagnosed and filled with anxiety. I'm glad I joined an educational webinar, it was very helpful."

6

Richter's transformation

43 Tests

44 Treatment

45 Key points

In a few people, chronic lymphocytic leukemia changes into an aggressive disease. This change is called Richter's transformation or Richter's syndrome. It can occur before or after treatment of chronic lymphocytic leukemia.

Tests

Tests are needed to confirm Richter's transformation and plan treatment. These tests are very similar to the tests for chronic lymphocytic leukemia (CLL) that are described in Chapter 2.

Confirming transformed CLL

High blood levels of lactate dehydrogenase (LDH) and Epstein-Barr virus can point to Richter's transformation. But a biopsy of lymph nodes is needed to confirm the diagnosis. A biopsy is a procedure that removes tissue samples from the body for testing.

Imaging may be used to select the best area to biopsy. Computed tomography (CT) and positron emission tomography (PET) are common scans. Options for imaging are a whole-body PET/CT scan or a diagnostic CT scan of the chest, abdomen, or pelvis.

A hematopathologist will examine and test the lymph node samples. They will look for signs

of transformation and if the transformed cells are related to CLL. Richter's transformation can evolve from mutations within CLL cells or from another B cell. If results aren't clear, bone marrow tests are often done next.

Planning cancer care

Your care team will ask about your current and past health to obtain your medical history. Your oncologist will examine your body and especially look for enlarged lymph nodes and organs. You will need to get blood draws, so a complete blood count (CBC) with differential and comprehensive metabolic panel can be done.

Additional tests on blood samples can help plan supportive care. Tests of LDH can help assess for autoimmune hemolytic anemia. Uric acid levels can show if you're likely to develop tumor lysis syndrome. Old viruses in your body may reactivate, so testing for Epstein-Barr and hepatitis viruses is useful. Read Chapter 5 for information on supportive care.

Depending on your treatment options, you might get a heart or human leukocyte antigen (HLA) test. An echocardiogram or multigated acquisition (MUGA) scan of your heart is needed to decide if a drug called anthracycline is safe. An HLA test is needed to find a donor for an allogeneic hematopoietic cell transplant.

Some cancer treatments can damage 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.

Treatment

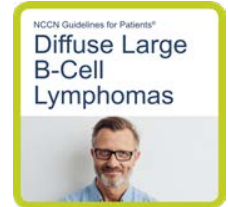
Richter's transformation has a poor outlook. Treatment is started right after diagnosis. The goal of treatment is to extend life.

Treatment is based on the type of lymphoma CLL transformed into. CLL most often transforms into diffuse large B-cell lymphoma (DLBCL). Less often, it changes into Hodgkin lymphoma.

DLBCL

Richter's transformation to DLBCL is generally treated with drug regimens for DLBCL. But which regimens are recommended depends on if DLBCL evolved from CLL cells or not. Also, new regimens may be available through clinical trials.

If DLBCL did not evolve from CLL cells, treatment recommendations for DLBCL are followed. These recommendations are available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



For DLBCL that evolved from CLL cells, a clinical trial is preferred. Ask your care team if there is an open trial that's a good fit for you. If a clinical trial is not an option, rituximab-based chemoimmunotherapy is often used for treatment, but BTK and immune checkpoint inhibitors are also options. **See Guide 7** for options.

Guide 7

Regimens for Richter's transformation from CLL cells to DLBCL

Chemoimmunotherapy

The DA-EPOCH-R regimen is dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab

The R-HyperCVAD regimen is rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine

The OFAR regimen is oxaliplatin, fludarabine, cytarabine, rituximab

The RCHOP regimen is rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

BTK inhibitors

Pirtobrutinib

Acalabrutinib

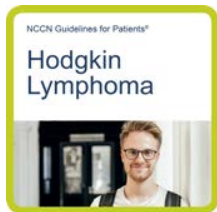
Immune checkpoint inhibitors

Nivolumab with or without ibrutinib

Pembrolizumab with or without ibrutinib

Hodgkin lymphoma

A clinical trial is the preferred treatment for Richter's transformation to Hodgkin lymphoma. The other option is recommended chemotherapy regimens. Treatment information for Hodgkin lymphoma is available at [NCCN.org/patientguidelines](https://www.nccn.org/patientguidelines) and on the [NCCN Patient Guides for Cancer](#) app.



Key points

- Richter's transformation is a change from CLL to an aggressive lymphoma. The diagnosis is confirmed with a biopsy of lymph nodes or bone marrow.
- Richter's transformation to DLBCL is typically treated with rituximab-based chemoimmunotherapy.
- Richter's transformation to Hodgkin lymphoma typically is treated with chemotherapy.

“

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.”

7

Making treatment decisions

- 47 It's your choice
- 47 Questions to ask
- 55 Resources

It is important to be comfortable with the cancer treatment you choose. This choice starts with having an open and honest conversation with your care team.

It's your choice

In shared decision-making, you and your care team share information, discuss the options, and agree on a treatment plan. It starts with an open and honest conversation between you and your team.

Treatment decisions are very personal. What is important to you may not be important to someone else.

Some things that may play a role in your decision-making:

- What you want and how that might differ from what others want
- Your religious and spiritual beliefs
- Your feelings about certain treatments
- Your feelings about pain or side effects
- Cost of treatment, travel to treatment centers, and time away from school or work
- Quality of life and length of life
- How active you are and the activities that are important to you

Think about what you want from treatment. Discuss openly the risks and benefits of specific treatments and procedures. Weigh options and share concerns with your care team. If you take the time to build a

relationship with your team, it will help you feel supported when considering options and making treatment decisions.

Second opinion

It is normal to want to start treatment as soon as possible. While cancer should not be ignored, there is time to have another care provider review your test results and suggest a treatment plan. This is called getting a second opinion, and it's a normal part of cancer care. Even doctors get second opinions!

Things you can do to prepare:

- Check with your insurance company about its rules on second opinions. There may be out-of-pocket costs to see doctors who are not part of your insurance plan.
- Make plans to have copies of all your records sent to the doctor you will see for your second opinion.

Support groups

Many people diagnosed with cancer find support groups to be helpful. Support groups often include people at different stages of treatment. Some people may be newly diagnosed, while others may be finished with treatment. If your hospital or community doesn't have support groups for people with cancer, check out the websites listed in this book.

Questions to ask

Possible questions to ask your care team are listed on the following pages. Feel free to use these or come up with your own. Be clear about your goals for treatment and find out what to expect from treatment.

Questions about cancer testing

1. What tests will I have?
2. Do the tests have any risks?
3. Will my insurance pay for all of the tests you are recommending?
4. Do I need to do anything to prepare for testing?
5. Should I bring someone with me to the appointments?
6. Where do I go for testing, and how long will it take?
7. If any of the tests will hurt, what will you do to make me comfortable?
8. How soon will I know the results and who will explain them to me?
9. How can I get a copy of the pathology report and other test results?
10. Is there an online portal with my test results?

Questions about CLL

1. What type of cancer do I have?
2. Is this an aggressive cancer?
3. What is the Rai or Lugano stage? Does this stage mean the cancer is advanced?
4. Does the cancer have any biomarkers? If yes, what do they mean?
5. Do I have to start treatment right away?
6. What can I do to be healthy if I don't need treatment right away?

Questions about treatment options

1. What are my treatment options?
2. Is a clinical trial an option for me?
3. What will happen if I do nothing?
4. Are you suggesting options other than what NCCN recommends? If yes, why?
5. How do my age, sex, overall health, and other factors affect my options?
6. What if I am pregnant, or planning to become pregnant?
7. Does any option offer a cure or long-term cancer control?
8. What are the side effects of the treatments?
9. How do I get a second opinion?
10. How long do I have to decide about treatment, and is there a social worker or someone who can help me decide?

Questions about what to expect

1. Does this hospital or cancer center offer the best treatment for me?
2. Do I have a choice of when to begin treatment?
3. How long will treatment last?
4. Who should I contact with questions or concerns if the office is closed?
5. How will you know if treatment is working?
6. What are the chances of the cancer worsening quickly?
7. What follow-up care is needed after treatment? What test results are important?

Questions about side effects

1. What are the possible complications and side effects of treatment?
2. Does the cancer itself cause any side effects?
3. Which side effects are most common and how long do they usually last?
4. Which side effects are serious or life-threatening?
5. Are there any long-term or permanent side effects?
6. What symptoms should I report right away, and who do I contact?
7. What can I do to prevent or relieve the side effects of treatment?
8. Do any medications worsen side effects?
9. Do any side effects lessen or worsen in severity over time?
10. Will you stop or change treatment if there are serious side effects?

Questions about clinical trials

1. Do you recommend that I consider a clinical trial for treatment?
2. How do I find clinical trials that I can participate in?
3. What are the treatments used in the clinical trial?
4. Has the treatment been used for other types of cancer?
5. What are the risks and benefits of this treatment?
6. What side effects should I expect and how will they be managed?
7. How long will I be in the clinical trial?
8. Will I be able to get other treatment if this doesn't work?
9. How will you know if the treatment is working?
10. Will the clinical trial cost me anything?

Resources

Bag It

bagitcancer.org

Be the Match

BeTheMatch.org/one-on-one

Cancer Hope Network

cancerhopenetwork.org

Centers for Disease Control and Prevention

cdc.gov/vaccines

CLL Society

cllsociety.org

Lymphoma Research Foundation

lymphoma.org

National Bone Marrow Transplant Link (nbmtLINK)

nbmtlink.org

National Coalition for Cancer Survivorship

canceradvocacy.org

The Leukemia & Lymphoma Society (LLS)

LLS.org/PatientSupport

Triage Cancer

Triagecancer.org

U.S. National Library of Medicine Clinical Trials Database

clinicaltrials.gov/



share with us.

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

NCCN.org/patients/comments

“

Meeting with and learning from other CLL patients is one of the best sources of emotional and educational support that I have seen. In a CLL support group, we can share our feelings, experiences, and encouragement with the only ones who are able to see CLL from the inside out - the patients!"



Words to know

allogeneic hematopoietic transplant

A cancer treatment that replaces abnormal blood stem cells with healthy donor cells.

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.

ASO-PCR

allele-specific oligonucleotide polymerase chain reaction

autoimmune hemolytic anemia

An attack on red blood cells by the disease-fighting (immune) system.

B cell

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

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.

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.

B symptoms

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

BTK

Bruton's tyrosine kinase

cancer stage

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

chemotherapy

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

chromosome

The structures within cells that package DNA and coded instructions for cell behavior (genes).

clinical trial

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

CLL

chronic lymphocytic leukemia

complete blood count (CBC)

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

comprehensive metabolic panel

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

computed tomography (CT)

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

contrast

A dye put into your body to make clearer pictures during imaging tests.

Words to know

deoxyribonucleic acid (DNA)

A chain of chemicals in cells that contains coded instructions for making and controlling cells. Also called the “blueprint of life.”

diagnosis

An identification of an illness based on tests.

differential

A lab test of the number of white blood cells for each type.

DLBCL

diffuse large B-cell lymphoma

echocardiogram

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

fatigue

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

FDA

Food and Drug Administration

fertility counselor

An expert who helps people to 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.

GVHD

graft-versus-host disease

HDMP

high-dose methylprednisolone

HLA

human leukocyte antigen

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 that is made by B cells to help fight off infection. Also called antibody.

immunohistochemistry (IHC)

A lab test that finds specific cancer cell markers involved in abnormal cell growth.

immunomodulator

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

International Prognostic Index (IPI)

A scoring system to assess the outlook of lymphoma.

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.

Lugano staging system

A rating scale of the outlook of small lymphocytic leukemia.

lymph

A clear fluid containing white blood cells.

lymph node

A small, bean-shaped, disease-fighting structure. Also called lymph gland.

Words to know

lymph vessel

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

lymphatic system

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

lymphocyte

One of three 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 lymph system.

medical history

A report of all your health events and medications.

MRD

minimal residual disease

multigated acquisition (MUGA) scan

A test that makes pictures of the heart.

next-generation DNA sequencing (NGS)

A lab test used to detect abnormal changes in DNA.

observation

A period of testing for changes in cancer status that signal treatment is needed.

pathologist

A doctor who's an expert in testing cells and tissue to find disease.

performance status

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

physical exam

A study of the body by a health expert for signs of disease.

PI3K

phosphoinositide 3-kinase

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 based on tests.

pure red cell aplasia

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

Rai staging system

A rating scale of the outlook of chronic lymphocytic leukemia.

reticulocyte

A young red blood cell that is formed in bone marrow and is present briefly in blood.

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 emotional response to treatment.

SLL

small lymphocytic lymphoma

spleen

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

supportive care

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

Words to know

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.

vaccine

A biological agent that is inserted into the body to prevent a disease.

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 1.2024. It was adapted, reviewed, and published with help from the following people:

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Abramson Cancer Center
at the University of Pennsylvania
Philadelphia, Pennsylvania
800.789.7366 • pennmedicine.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
CC Taussig Cancer Institute
866.223.8100 • my.clevelandclinic.org/departments/cancer
Case CCC
216.844.8797 • case.edu/cancer

City of Hope National Medical Center
Duarte, California
800.826.4673 • cityofhope.org

**Dana-Farber/Brigham and Women's Cancer Center |
Mass General Cancer Center**
Boston, Massachusetts
617.732.5500 • youhaveus.org
617.726.5130 • massgeneral.org/cancer-center

Duke Cancer Institute
Durham, North Carolina
888.275.3853 • dukecancerinstitute.org

Fox Chase Cancer Center
Philadelphia, Pennsylvania
888.369.2427 • foxchase.org

Fred & Pamela Buffett Cancer Center
Omaha, Nebraska
402.559.5600 • unmc.edu/cancercenter

Fred Hutchinson Cancer Center
Seattle, Washington
206.667.5000 • fredhutch.org

Huntsman Cancer Institute at the University of Utah
Salt Lake City, Utah
800.824.2073 • healthcare.utah.edu/huntsmancancerinstitute

**Indiana University Melvin and Bren Simon
Comprehensive Cancer Center**
Indianapolis, Indiana
888.600.4822 • www.cancer.iu.edu

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

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Memorial Sloan Kettering Cancer Center
New York, New York
800.525.2225 • mskcc.org

Moffitt Cancer Center
Tampa, Florida
888.663.3488 • moffitt.org

O'Neal Comprehensive Cancer Center at UAB
Birmingham, Alabama
800.822.0933 • uab.edu/onealcancercenter

**Robert H. Lurie Comprehensive Cancer
Center of Northwestern University**
Chicago, Illinois
866.587.4322 • cancer.northwestern.edu

Roswell Park Comprehensive Cancer Center
Buffalo, New York
877.275.7724 • roswellpark.org

**Siteman Cancer Center at Barnes-Jewish Hospital
and Washington University School of Medicine**
St. Louis, Missouri
800.600.3606 • siteman.wustl.edu

**St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center**
Memphis, Tennessee
866.278.5833 • stjude.org
901.448.5500 • uthsc.edu

Stanford Cancer Institute
Stanford, California
877.668.7535 • 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

**The Sidney Kimmel Comprehensive
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Baltimore, Maryland
410.955.8964
www.hopkinskimmelcancercenter.org

The UChicago Medicine Comprehensive Cancer Center
Chicago, Illinois
773.702.1000 • uchicagomedicine.org/cancer

The University of Texas MD Anderson Cancer Center
Houston, Texas
844.269.5922 • mdanderson.org

UC Davis Comprehensive Cancer Center
Sacramento, California
916.734.5959 • 800.770.9261
health.ucdavis.edu/cancer

NCCN Cancer Centers

UC San Diego Moores Cancer Center

La Jolla, California

858.822.6100 • cancer.ucsd.edu

UCLA Jonsson Comprehensive Cancer Center

Los Angeles, California

310.825.5268 • uclahealth.org/cancer

UCSF Helen Diller Family Comprehensive Cancer Center

San Francisco, California

800.689.8273 • cancer.ucsf.edu

University of Colorado Cancer Center

Aurora, Colorado

720.848.0300 • coloradocancercenter.org

University of Michigan Rogel Cancer Center

Ann Arbor, Michigan

800.865.1125 • rogelcancercenter.org

University of Wisconsin Carbone Cancer Center

Madison, Wisconsin

608.265.1700 • uwhealth.org/cancer

UT Southwestern Simmons Comprehensive Cancer Center

Dallas, Texas

214.648.3111 • utsouthwestern.edu/simmons

Vanderbilt-Ingram Cancer Center

Nashville, Tennessee

877.936.8422 • vicc.org

Yale Cancer Center/Smilow Cancer Hospital

New Haven, Connecticut

855.4.SMILOW • yalecancercenter.org

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BSES MG Hospital (Andheri):

9 am to 10 am (Monday to Friday)

Nanavati Max Hospital (Vile Parle):

10 am to 12 pm (Monday to Saturday)

S. L. Raheja Hospital (Mahim):

12 pm to 4 pm (Monday to Saturday)

Suvarna Hospital (Borivali):

5 pm to 6 pm (Monday and Friday)

Sushrut Hospital (Chembur):

By appointment

Hinduja Hospital (Khar): By

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Galaxy Healthcare (Borivali): By

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