Chronic Lymphocytic Leukemia
It's easy to get lost in the cancer world

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✓ Step-by-step guides to the cancer care options likely to have the best results
✓ Based on treatment guidelines used by health care providers worldwide
✓ Designed to help you discuss cancer treatment with your doctors
These NCCN Guidelines for Patients are based on the NCCN Guidelines® for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2022 – January 18, 2022.

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Chronic lymphocytic leukemia (CLL) is a type of blood cancer. Read this chapter to learn about leukemia and how CLL differs from other leukemias.

What is leukemia?

Leukemia and other blood cancers affect how blood cells are made and work. There are 3 main types of blood cells:

- Red blood cells (also called erythrocytes)
- White blood cells (leukocytes)
- Platelets (thrombocytes)

Red blood cells carry oxygen throughout the body. White blood cells help fight germs. Platelets help control bleeding.

Leukemia is the most common type of blood cancer. It is a cancer of white blood cells or cells that become white blood cells.

Leukemia cells form in bone marrow

Most bones have a soft center called marrow. Inside bone marrow are hematopoietic (blood) stem cells. Blood stem cells create all blood cells. They form into either lymphoid or myeloid progenitor cells. Progenitor cells make young blood cells called blasts. Blasts become mature blood cells.

Myeloblasts are young myeloid cells that form into 2 types of white blood cells:

- Granulocytes, which include basophils, neutrophils, and eosinophils
- Monocytes

Types of white blood cells

White blood cells are part of myeloid and lymphoid cell lines. Basophils, neutrophils, and eosinophils are myeloid cells called granulocytes. Monocytes are another type of myeloid cell. B lymphocytes, T lymphocytes, and natural killer cells are lymphoid cells called lymphocytes.
Lymphoblasts are young lymphoid cells that form into lymphocytes. There are 3 types of lymphocytes:

- B lymphocytes (also called B cells)
- T lymphocytes (T cells)
- Natural killer cells

Leukemia is a type of cancer that causes many abnormal white blood cells to form in bone marrow. The abnormal blood cells are called leukemia cells. Leukemia cells may fill up bone marrow leaving little room for healthy blood cells to grow.

**Leukemia cells enter the bloodstream**

Normally, mature blood cells leave the bone marrow and enter the bloodstream. From the bloodstream, blood cells are released into body tissues.

Likewise, leukemia cells leave marrow and enter the bloodstream. The leukemia cells are young or partly mature blood cells. They don’t work as they should.

**Leukemia cells may build up in the lymph system**

The bloodstream transports mature lymphocytes to the lymph (or lymphatic) system. The lymph system is a network of tissues that have many white blood cells and a fluid called lymph.

Lymph travels in a “superhighway” of tube-shaped vessels that are throughout the body. As it travels, it passes through lymph nodes (also called “glands”). Lymph nodes filter out germs and waste.

Leukemia cells may also travel into the lymph system. The leukemia cells can build up in lymph tissue causing the tissue to...
swell. Enlarged lymph nodes are a common symptom of leukemia.

What are the types of leukemia?

There are many types of leukemia. They differ by which type of blood cell is affected. How fast the leukemia worsens is partly based on the affected blood cell.

**Acute leukemia**
Acute leukemia often worsens quickly and causes symptoms. Treatment is often needed right away.

Acute leukemia affects immature blood cells. The immature blood cells make leukemia cells that are unable to develop into mature cells.

- Acute lymphoblastic leukemia (ALL) affects lymphoid cells that make many abnormal lymphoblasts.
- Acute myeloid leukemia (AML) affects myeloid cells that make many abnormal myeloblasts.

**Chronic leukemia**
Chronic leukemia often worsens slowly over time. People with chronic leukemia may not have symptoms or need treatment right away. Chronic leukemia affects mature blood cells.

- Chronic lymphocytic leukemia (CLL) affects lymphoid cells that make many abnormal B cells.
- Chronic myeloid leukemia (CML) affects myeloid cells that make many abnormal granulocytes.

How do CLL and SLL differ?

CLL is the most common leukemia in adults. It is a cancer of B cells. The B cells look almost normal but don’t function correctly. They can’t fight infections well. CLL often worsens slowly, but for some people it worsens quickly.

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

- With CLL, many leukemia cells are found in the blood and bone marrow. Leukemia cells may also be in the lymph nodes and spleen.
- With SLL, there are few, if any, leukemia cells in the blood. Instead, the leukemia cells are mainly in lymph nodes and the spleen.

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

How is CLL found?

Most often, CLL is found because of routine blood work. A complete blood count (CBC) is a common blood test that measures the number of blood cells. A high number of lymphocytes is often the first sign of CLL.

Less often, CLL is found because of painless, swollen lymph nodes. Swollen lymph nodes may get smaller then swell up again. Swelling of lymph nodes often occurs in multiple parts of the body.

Most people don’t have symptoms of CLL at diagnosis. When people do have symptoms, health care providers might not suspect cancer at first. Symptoms of CLL are caused by...
other health problems, too. Take fatigue, for example. It is a common symptom of CLL, but it is also caused by anemia, stress, inactivity, and some medications.

If your health care provider suspects CLL, more testing is needed. Getting a diagnosis of CLL can be a shock especially if you feel healthy.

This book explains treatment options for CLL. Treatment for CLL has greatly improved in recent years. For many people, treatment can keep CLL under control for long periods of time. Discuss the treatments in this book with your doctor. Together, you can make a treatment plan that’s best for you.

Review

- Leukemia is a cancer of white blood cells or cells that become white blood cells. Leukemia cells are often found in bone marrow, blood, and lymph tissue.
- Acute leukemia worsens quickly. Chronic leukemias often worsen slowly.
- CLL is a type of chronic leukemia. It is a cancer of B lymphocytes.
- CLL and SLL are the same cancer. They differ by the location of the cancer cells. Treatment of the cancers is very similar because the cancer cells are the same.
- Tests of CLL may be done because of high lymphocyte counts, swollen nodes, or symptoms.
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Tests for CLL

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If your doctor suspects that you have CLL, several tests are needed. There are many types of B cell cancers, so it is important that the right tests are done. This chapter describes the tests used to diagnose CLL and plan treatment.

**Cancer tests**

The only way to be sure that you have chronic lymphocytic leukemia (CLL) is to test fluid or tissue samples from your body. Most often, CLL is found (diagnosed) by testing a blood sample. The tests needed to diagnose and plan treatment are described on the next pages and are listed in Guide 1.

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 CLL doctor. Ask for a copy. It is used to plan your treatment. Your doctor will review the results with you. Take notes and ask questions.

**Diagnosis by blood test**

The hematopathologist will examine a drop of your blood using a microscope. This is called a blood smear. Your CLL doctor may also view the blood smear. The features of the leukemia

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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.

**Diagnosis by biopsy**

A biopsy is a procedure that removes tissue samples from the body. If needed, samples of lymph nodes or bone marrow can be tested to diagnose CLL.

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 method called immunohistochemistry (IHC) will be used to find the immunophenotype of the biopsied cells.

**Test results needed to diagnose CLL**

A diagnosis of CLL is made based on 3 test results:

- The leukemia cells have a CLL immunophenotype, which includes CD5, CD19, and CD23, some CD20, and no CD10 proteins.
- The leukemia cells are copies of the same cancer cell, which is called monoclonality.
- There are at least 5,000 monoclonal B lymphocytes in blood (5 x 10⁹/L).

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**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 is helpful for identifying the correct type of cancer. For instance, CLL cells have proteins called CD200 and LEF1, but mantle cell lymphoma does not have them.

Genetic biomarkers

Genetic information tells your cells what to do. It is located in the nucleus of a cell and stored in 46 long strands of DNA. A gene is a small segment of DNA. Strands of DNA are carried and packaged in 23 chromosomes.

Doctors look for genetic biomarkers to predict the outlook (prognosis) of CLL. The biomarkers are found with 3 lab tests on either a blood or bone marrow sample:

- Fluorescence in situ hybridization (FISH) can show missing parts of chromosomes and extra chromosomes. In CLL, the leukemia cells may have 11q, 13q, or 17p deletions. The cells may have an extra copy of chromosome 12 also called trisomy 12.
- DNA sequencing is used to look for mutations in the \textit{TP53} and \textit{IGHV} genes.
- A karyotype can show defects in chromosomes. A complex karyotype is 3 or more unrelated defects in chromosomes that occur in more than one cell.

Genetic information

The nucleus is the control center or “brain” of cells. Within the nucleus is genetic information that tells the cells what to do. The information is stored in DNA, which looks like a twisted ladder. Genes are parts of DNA that contain “instructions” for the cell. At times, strands of DNA tightly coil and form into chromosomes.
Health history

Expect your doctor to review your health in detail. This is known as taking a medical history. Your doctor 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.” B symptoms are fevers when there’s no infection, heavy night sweats, and unexplained weight loss.

Some cancers and other health conditions can run in families. Be prepared to discuss the health problems 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 doctor will also 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, including your spleen and liver
- Assessing your level of pain, if any, when you are touched

Checking for swelling
Leukemia cells can build up in lymph nodes, the spleen, and the liver causing them to swell. Your doctor will gently press on your body to assess their size. Areas that may be touched include your neck, armpit, belly, and groin.

Checking your physical ability
Based on your history and exam, your doctor will rate your performance status. Performance status is your ability to do day-to-day activities. The Eastern Cooperative Oncology Group (ECOG) Performance Status is a common scoring system. It consists of five scores. Lower scores represent a higher ability to take care of yourself.

Blood tests

Blood tests can measure blood cells, proteins, and chemicals in the bloodstream. Samples of your blood will be removed with a needle that is inserted into a vein. This is called a blood draw. You may need to fast from food and most liquids for hours before the draw.

CBC with differential
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.

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

Other blood tests
Some people with CLL may get other blood tests. Other elements in the blood that may be measured are:

- Quantitative immunoglobulins to assess your risk of infections
- Haptoglobin, reticulocytes, and Coombs tests to assess if your body is attacking your red blood cells
Tests for CLL

### Bone marrow tests

Tests on bone marrow are not often needed to diagnose CLL. They may be done to assess how many leukemia cells are in marrow. There are two methods of removing bone marrow.

- A bone marrow biopsy removes a core of bone and soft bone marrow.
- A bone marrow aspiration removes liquid bone marrow.

These procedures may be done at the same time. The samples will be sent to a hematopathologist for testing.

### Guide 2

#### Tests for CLL that may be useful

| Blood tests                                | • Quantitative immunoglobulins  
|                                           | • Reticulocyte count, haptoglobin, and direct antiglobulin (Coombs) test  
|                                           | • Beta-2 microglobulin  
|                                           | • LDH  
|                                           | • Uric acid  
|                                           | • Hepatitis B and hepatitis C test  
| Bone marrow tests                          | • Bone marrow biopsy and aspirate  
| Imaging                                   | • Diagnostic CT of chest, abdomen, and pelvis if needed  
|                                           | • PET/CT to guide biopsy of lymph node if Richter’s transformation is suspected  
| Heart test                                | • Echocardiogram or MUGA scan if needed  
| Fertility and pregnancy                   | • Pregnancy test  
|                                           | • Fertility counseling as needed  

A complete list of tests that may be useful are listed in Guide 2.
Imaging

Imaging takes pictures of the insides of your body. It is sometimes used to detect cancer that is deep in the body. Not all people with CLL will need imaging.

Diagnostic CT
Computed tomography (CT) makes a more detailed image than a plain x-ray. It takes many pictures of your body from different angles using x-rays. A computer then combines the pictures to make a 3D image.

Contrast and a higher dose of radiation are used for a diagnostic CT. Blood vessels, organs, and other tissues are more clearly seen. Contrast is injected into the bloodstream and leaves the body in urine.

Diagnostic CT of your chest, abdomen, and pelvis may be needed for 2 reasons. One reason is to look for enlarged lymph nodes that may be causing symptoms. Another reason is to assess the extent of the cancer before starting a treatment called venetoclax. Venetoclax can cause a rare but serious health problem called tumor lysis syndrome.

PET/CT-directed needle biopsy
Sometimes CT is combined with PET (positron emission tomography). PET can detect even small amounts of cancer with a radiotracer and special camera. PET/CT is useful if your doctor thinks that CLL is turning into a fast-growing cancer called Richter’s transformation. It can show the best area to biopsy. The removed tissue will be tested to confirm if the leukemia has changed.

Heart test

A type of cancer drug called anthracycline may damage your heart. It is used to treat CLL that has transformed into a faster-growing cancer. To plan treatment, your doctor may test how well your heart pumps blood. You may get an echocardiogram or multigated acquisition (MUGA) scan. An echocardiogram uses ultrasound to make pictures of your heart. A MUGA scan makes pictures using an injected radiotracer and special camera.

“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!”

– Barbara
Fertility and pregnancy

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

**Fertility counseling**
Fertility is the ability to have a baby. Some cancer treatments can damage the body parts needed for fertility. Ask your cancer doctor 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 after treatment. Collecting and freezing sperm or eggs is a common method.

**Pregnancy test**
Some cancer treatments can harm an unborn baby. Get a pregnancy test before treatment if you may be pregnant. Your treatment options will depend on the results.

**Birth control**
During treatment, don’t get pregnant or get someone pregnant. Take steps to prevent pregnancy. Your cancer care team can tell you which birth control methods are best to use.

Review

- A diagnosis of CLL is made based on tests of blood, lymph nodes, or bone marrow. Hematopathologists look for very high numbers of abnormal B cells. They also look for protein markers that are common and uncommon to CLL cells.
- CLL doctors use genetic biomarkers to assess prognosis and plan treatment.
- Be ready to tell your cancer care team about any health problems and treatments you’ve had in your lifetime.
- Tell your team about any recent fevers, night sweats, and unexplained weight loss. These can be symptoms of CLL.
- Your CLL doctor will rate your ability to do day-to-day activities in order to decide your treatment options.
- Your CLL doctor will order blood tests and use the results to plan treatment.
- Your bone marrow may be tested to find the cause of low blood cell counts.
- Imaging allows doctors to look inside your body for cancer in tissue.
- You may get a heart test to see if you’re healthy enough to have certain cancer treatments.
- Ask your CLL doctor if you are at risk for impaired fertility. There are ways to have a healthy baby after cancer treatment.
- Before starting treatment, get a pregnancy test. Some cancer treatments can harm unborn babies.
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3 Watch and wait

Waiting is safe

You may start treatment for CLL months or years after diagnosis. Some people never start treatment.

CLL is unlike many cancers. It often worsens very slowly. It is commonly found before it causes symptoms. Years may pass before CLL worsens to the point of needing treatment. Many people with CLL have normal lifespans.

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. There are 3 main reasons for delaying treatment:

- Early treatment of CLL does not lengthen life.
- Treatment may cause health problems called side effects.
- 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. During watch and wait, your cancer 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.

NCCN has resources to help you during watch and wait. NCCN has a two-part book series on survivorship care. A person is a cancer survivor starting at diagnosis and through the balance of their life. The survivorship book on healthy living focuses on:

- Being physically active and avoiding inactivity
- Eating healthful foods
- Limiting or avoiding drinking alcohol
- Achieving and maintaining a normal body weight
- Not using tobacco
- Avoiding infections and getting safe vaccines (there is also information on vaccines in Chapter 5 of this book)
Read about preventing poor health in *NCCN Guidelines for Patients: Survivorship Care for Healthy Living*, available at [NCCN.org/patientguidelines](http://NCCN.org/patientguidelines).

The other survivorship book addresses late and long-term effects of cancer and treatment. Such effects include second cancers, fatigue, poor sleep, and heart disease. Read about common effects in *NCCN Guidelines for Patients: Survivorship Care for Cancer-Related Late and Long-Term Effects*, available at [NCCN.org/patientguidelines](http://NCCN.org/patientguidelines).

Everyone with cancer has some distress at some point in time. Distress is normal. Read about treating distress in *NCCN Guidelines for Patients: Distress During Cancer Care*, available at [NCCN.org/patientguidelines](http://NCCN.org/patientguidelines).

"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."

– Ted
When to start treatment

Talk with your CLL doctor about starting treatment. Share your wishes and concerns. Your doctor will assess starting treatment based on the cancer stage, signs, and symptoms.

Rai stages

A cancer stage is a rating by your cancer care provider that suggests the outcome of the cancer. The Rai staging system is commonly used for CLL. It 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 Rai staging system is based on how lymphocytes are affecting the body. In all stages, there are many abnormal lymphocytes in the body. In stage 0, the lymphocytes are not having a major effect on lymphoid tissue, the liver, or bone marrow. In stages 1 and 2, the lymphocytes are causing swelling of the lymph nodes, spleen, or liver. In stages 3 or 4, the lymphocytes in bone marrow are causing a drop in the number of red blood cells or platelets. The criteria for each stage are listed in Guide 3.

Guide 3
Criteria for Rai stages of CLL

<table>
<thead>
<tr>
<th>Rai 0</th>
<th>Rai 1</th>
<th>Rai 2</th>
<th>Rai 3</th>
<th>Rai 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Many lymphocytes (lymphocytosis)</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Enlarged lymph nodes (lymphadenopathy)</td>
<td></td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Enlarged spleen, liver, or both (organomegaly)</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Low numbers of red blood cells (anemia)</td>
<td></td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Low numbers of platelets (thrombocytopenia)</td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>

● required criterion  ● may occur
The 5 stages can be condensed into 3 risk groups:

- Stage 0 has a **low risk** of getting worse.
- Stages 1 and 2 have an **intermediate** risk of getting worse.
- Stages 3 and 4 have a **high risk** of getting worse.

**Reasons to treat**

In general, treatment is started when the effects of cancer become worse than the risks of its 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 by Rai stage in **Guide 4**.

### Guide 4

**Reasons to start treatment**

<table>
<thead>
<tr>
<th>Rai stage 0</th>
<th>Rai stage 1</th>
<th>Rai stage 2</th>
</tr>
</thead>
</table>
| You can enroll in a clinical trial | You have major symptoms of CLL  
  • 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  
The size of your spleen or lymph nodes is growing quickly or causing discomfort  
CLL is causing the number of red blood cells to decrease  
CLL is causing the number of platelets to decrease  
Your body is killing your blood cells (autoimmune cytopenia) and treatment with steroids is not working |
| Rai stage 3 | Rai stage 4 | The number of blood cells is low (cytopenia) and getting lower |
Review

- Early treatment of CLL does not lengthen life. Clinical trials are testing if starting new treatments early will improve results.
- Your doctors will regularly check the status of CLL during watch and wait.
- You can take care of your health by going to appointments, finding support, and living healthfully.
- Treatment is started based on your wishes and the stage, signs, and symptoms of CLL.

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
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There have been several breakthroughs in the treatment of CLL. Newer treatments are better at controlling the cancer and improving quality of life. Despite improved treatment, a cure is still needed. Better treatments are made possible with clinical trials.

**Beyond chemotherapy**

Treatment for CLL has greatly improved in recent years. Newer treatments target how leukemia cells live, survive, and die. This section describes some of the advances in treatment.

**Chemotherapy**

Chemotherapy alone was once the standard treatment of CLL. Sometimes, it didn't have great results. Chemotherapy is a term for drugs that kill rapidly dividing cells. In general, cancer cells rapidly divide but so do some normal cells. The death of normal cells often causes health problems during chemotherapy. Health problems caused by treatment are called side effects. All cancer treatments have side effects. Newer treatments for CLL affect healthy cells less so than chemotherapy. They can cause serious side effects but have fewer serious side effects than chemotherapy.

Chemotherapy is now used with other cancer drugs. If your health is fairly good, your treatment may include a purine analogue. Purine analogues include fludarabine, cladribine, and pentostatin. If your health is poor, you may receive chemotherapy drugs called alkylating agents. Other types of chemotherapy may be used if CLL transforms into a cancer called lymphoma.

**Antibody treatment**

Antibody treatment has been a major advance in the management of CLL. Antibodies are proteins made by the body. They can also be made by people in a lab to treat cancer. Antibodies for CLL are designed to attach to proteins on cancer cells. They mark the cells so that the immune system can find and destroy them. They are a type of immunotherapy.

The most common antibody treatment for CLL targets CD20. CD20 is a protein that is only on the surface of B cells. CD20 antibodies include obinutuzumab (Gazyva), ofatumumab (Arzerra), and rituximab (Rituxan). They may be used alone or with other medications to treat CLL.

Chemoimmunotherapy for CLL consists of chemotherapy and CD20 antibodies. It produces excellent results in a subset of people with CLL. Not everyone with CLL can take chemoimmunotherapy. It may cause too many side effects or won’t work.

Another antibody used to treat CLL is alemtuzumab (Campath). It is a CD52 antibody. CD52 is on the surface of T cells and B cells. Alemtuzumab has had good results in a subset of people for whom CD20 antibodies are not an option. It is not used much due to its side effects and since there are other good treatment options.
**BCR pathway blockers**
The B cell receptor (BCR) is a protein on the surface of B cells. It triggers a chemical pathway in B cells that signals for the cells to stay alive and make new cells. Cancer drugs that block the BCR pathway are a breakthrough in the treatment of CLL. Blocking the BCR pathway causes the cells to die.

Bruton’s tyrosine kinase (BTK) inhibitors are a key treatment of CLL. BTK is a protein in the BCR pathway. BTK inhibitors block BTK, which stops the growth signal from BCR. Acalabrutinib (Calquence), ibrutinib (Imbruvica), and zanubrutinib (Brukinsa) are BTK inhibitors.

PI3K is another protein in the BCR pathway. PI3K inhibitors block PI3K and stop BCR growth signals. Idelalisib (Zydelig) targets one form of PI3K called delta. Duvelisib (Copiktra) targets two forms of PI3K—delta and gamma.

**BCL-2 pathway blockers**
BCL-2 is a protein inside of B cells that helps prevent cell death. In CLL, BCL-2 may build up and stop the cancer cells from dying. Venetoclax (Venclexta) is a BCL-2 inhibitor that allows the cancer cells to self-destruct. It can cause severe side effects.

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**Improving treatment**

Despite advances in treatment, more research is needed. Research is needed because current treatments rarely cure CLL. Without a cure, many people live with side effects from long-term treatment. Other people stop treatment then restart when CLL worsens. People with CLL are at risk of life-threatening infections.

**Clinical trials**

A clinical trial 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 doctor 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 I 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 II trials** study how well the drug or approach works against a specific type of cancer.

- **Phase III trials** test the drug or approach against a standard treatment. If the
results are good, it may be approved by the FDA.

- **Phase IV 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 whom 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 doctor 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 treatment 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—insurance. You are responsible for copays and any costs for this care that are not covered by your insurance.

Review
- Chemotherapy by itself does not produce great results in CLL. It also can cause several severe side effects.
- Several advances in treatment have been made. Newer treatments include immunotherapy, BTK and PI3K inhibitors, and BCL-2 inhibitors.
- Despite advances in treatment, a cure for CLL is still needed.
- Clinical trials test potential new ways of fighting cancer in people.
- Ask your treatment team about the option of a clinical trial.
5 Treatment of CLL

32 Biomarkers
33 First-line treatment
36 Supportive care
38 Treatment response
40 Second-line treatment
42 Richter’s transformation
43 Review
Not everyone with CLL receives the same treatment. Discuss the options in this chapter with your doctor. Your doctor will tailor treatment to you and the cancer you have.

### Biomarkers

CLL differs between people. Differences in how CLL behaves are caused by biomarkers. Because CLL biomarkers differ between people, a treatment that helps one person might not help you.

Some biomarkers may change during watch and wait and after treatment starts. Before each line of treatment, your doctor should test the cancer cells again. There are 4 important lab tests:

- Fluorescence in situ hybridization (FISH) for 17p deletion
- DNA sequencing for TP53 mutation
- DNA sequencing for IGHV mutation if not done before
- CpG-stimulated karyotype for complex genetic changes

#### 17p deletion

One biomarker that differs between people with CLL is called 17p deletion. A 17p deletion is a missing part of chromosome 17. It is sometimes written as del(17p). When 17p is deleted, a gene called TP53 is deleted, too.

The TP53 gene contains instructions for building a protein called p53. The p53 protein is needed to repair damaged DNA and start the process for cells beyond repair to die. p53 is absent in CLL cells if there is a 17p deletion. When absent, chemotherapy will likely not be an effective treatment.

#### TP53 mutation

In CLL cells that have 17p, the TP53 gene may be mutated. A mutated TP53 gene causes the p53 protein to be abnormal and not work as it should. When mutated, chemotherapy will likely not be an effective treatment.

#### IGHV mutation

Mutations in leukemia cells are almost always a bad thing. One exception is mutated IGHV region genes that cause mutated IGHV receptors. These mutations mean the leukemia cells may have formed from more mature B cells. When B cells are more mature, CLL worsens more slowly and responds better to chemotherapy. If not done before, testing for IGHV mutation status is needed before first-line treatment.

#### Complex karyotype

A complex karyotype is 3 or more unrelated defects in chromosomes that occur in more than one cell. A complex karyotype suggests worse outcomes, but more research is needed. Prognosis may depend on the type of defect, number of defects, and combination of defects in the cells. In fact, some complex karyotypes may suggest a good outcome. But, in general, a complex karyotype may limit how well BTK inhibitors work.
First-line treatment

Before first-line treatment, you may undergo imaging. Imaging is done to see if lymph nodes, the spleen, and the liver are enlarged. Doctors use imaging to make decisions about cancer treatment and outlook.

There are multiple good treatment options for CLL. Your doctor will plan treatment for you based on:

- Your age
- Your overall health and medications
- Biomarkers
- Length of remission achieved by treatments
- Your wishes for time-limited treatment and at-home treatment

A key factor for deciding treatment options is whether there is a 17p deletion or TP53 mutation. These biomarkers are uncommon in people with CLL who have not had treatment.

Clinical trials

Clinical trials are a type of research. Within clinical trials, new ways of treating cancer are tested. Treatment of CLL has greatly improved because of clinical trials.

More clinical trials are needed to find better ways to treat CLL. It is unknown in what order treatments should be taken to get the best results. Research on combinations of treatments is also needed.

NCCN experts recommend clinical trials, especially if leukemia cells have 17p deletion or a TP53 mutation. Even with newer treatments, outcomes for CLL with either marker are worse than other CLL types. Clinical trials are key to finding better treatments.

Preferred regimens

Bruton’s tyrosine kinase (BTK) inhibitors are central to the treatment of CLL. They block signals from the B cell receptor (BCR). They are pills and can be taken at home. They are taken for as long as they are working.

The first BTK inhibitor used to treat CLL was ibrutinib. Ibrutinib often has very good results. Sometimes, it causes serious side effects including heart disease.

Acalabrutinib is a newer BTK inhibitor. Acalabrutinib was developed to have fewer side effects than ibrutinib. Research is underway to compare the 2 treatments.

It is essential to have a doctor that you trust implicitly, and who knows that you are the ultimate decision-maker in your treatment regimen. If you can’t advocate for yourself, ask a family member or friend for help.”

– Dixie
Zanubrutinib is the newest BTK inhibitor. It may be an option when other BTK inhibitors are not options due to side effects.

Obinutuzumab may be added to acalabrutinib. It is slowly injected into a vein (infusion) at a health care center.

Venetoclax with obinutuzumab is a newer first-line treatment. Venetoclax is a BCL-2 inhibitor. In the short term, venetoclax with obinutuzumab has had good results. Research on long-term results is needed.

Some people with CLL may prefer venetoclax over BTK inhibitors. It is taken for 1 year and reduces CLL to very low levels. Taking venetoclax for a fixed time may prevent CLL from becoming resistant to it. BTK inhibitors or venetoclax are preferred for patients who have 17p deletion or TP53 mutation.

Other regimens
For CLL without 17p deletion and TP53 mutation, chemoimmunotherapy is a common treatment. An alkylating agent—bendamustine or chlorambucil—with a CD20 antibody may be an option. If you are younger than 65 years of age and healthy enough, fludarabine-based chemoimmunotherapy may be recommended. Fludarabine, cyclophosphamide, and rituximab (FCR) works well in a subset of people.

For CLL with 17p deletion or TP53 mutation, chemotherapy does not work well. Treatment with BTK inhibitors or venetoclax has better results. Additionally, the antibody, rituximab, may be combined with high-dose methylprednisolone (HDMP) if BTK inhibitors or venetoclax are no longer working.

All options for first-line regimens are listed in Guide 5 and Guide 6.
### Guide 5
**First-line regimens for CLL without 17p deletion and TP53 mutation**

<table>
<thead>
<tr>
<th>Preferred regimens</th>
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<tbody>
<tr>
<td>• Acalabrutinib with or without obinutuzumab</td>
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<td>• Ibrutinib</td>
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<tr>
<td>• Venetoclax and obinutuzumab</td>
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<tr>
<td>• Zanubrutinib</td>
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<tr>
<th>Other regimens for people who are 65 years of age and over or who have major health conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bendamustine and an anti-CD20 monoclonal antibody if you are not frail</td>
</tr>
<tr>
<td>• Chlorambucil and obinutuzumab</td>
</tr>
<tr>
<td>• High-dose methylprednisolone (HDMP) and either rituximab or obinutuzumab</td>
</tr>
<tr>
<td>• Ibrutinib and obinutuzumab</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
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<table>
<thead>
<tr>
<th>Other regimens for people who are under 65 years of age and fairly healthy</th>
</tr>
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<tbody>
<tr>
<td>• Bendamustine and an anti-CD20 monoclonal antibody</td>
</tr>
<tr>
<td>• Fludarabine, cyclophosphamide, and rituximab (FCR; preferred among other regimens for CLL with IGHV mutations)</td>
</tr>
<tr>
<td>• Fludarabine and rituximab</td>
</tr>
<tr>
<td>• HDMP and rituximab</td>
</tr>
<tr>
<td>• Ibrutinib and rituximab</td>
</tr>
</tbody>
</table>

### Guide 6
**First-line regimens for CLL with 17p deletion or TP53 mutation**

<table>
<thead>
<tr>
<th>Preferred regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acalabrutinib with or without obinutuzumab</td>
</tr>
<tr>
<td>• Ibrutinib</td>
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</tr>
<tr>
<td>• Zanubrutinib</td>
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<table>
<thead>
<tr>
<th>Other regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alemtuzumab with or without rituximab</td>
</tr>
<tr>
<td>• High-dose methylprednisolone (HDMP) and rituximab</td>
</tr>
<tr>
<td>• Obinutuzumab</td>
</tr>
</tbody>
</table>
Supportive care

Supportive care aims to improve your quality of life. It is sometimes called palliative care. It is a key part of treatment for everyone, not just people at the end of life. Talk with your treatment team to get the best supportive care for you.

Supportive care is an important part of your cancer care. It can address many needs. It includes care for health issues caused by cancer or cancer treatment. You can get help with making treatment decisions. You can get help with coordination of care between health providers. Guide 7 lists some of the supportive needs of people with CLL.

All cancer treatments can cause health issues called side effects. Some side effects of CLL treatments are listed in Guide 7. Ask your treatment team for a list of side effects of your treatments. During and after treatment, tell your team about any new or worse symptoms. There may be ways to help you feel better. Sometimes, a treatment may be stopped until you are better and then restarted.

Infections
You are more likely to get infections due to CLL or its treatment. Get a flu shot every year and a pneumococcal polysaccharide vaccine every 5 years. But, don’t get a live virus vaccine. If needed, also get the recombinant, adjuvanted zoster vaccine (Shingrix) to prevent shingles.

COVID vaccinations are also recommended for all people with CLL. Any of the COVID vaccines are safe and help to prevent serious illness. But, the vaccines may not work as well in people with CLL. Keep wearing a mask and avoid crowds, even after getting vaccinated. Learn more at NCCN.org/covid-19.

If you get frequent infections in your ear, sinuses, or lungs, you may need immunoglobulin infusions to help prevent new infections.

Some people with CLL take medicine to prevent herpes and pneumocystis jirovecii pneumonia. These infections are more likely when taking purine analog- or bendamustine-based chemoimmunotherapy or alemtuzumab.

Hepatitis and cytomegalovirus
Hepatitis B and cytomegalovirus may be reactivated during cancer treatment. Hepatitis B may be reactivated when taking CD20 antibodies or chemotherapy. Cytomegalovirus may be reactivated when taking PI3K inhibitors and alemtuzumab. Reactivation may be prevented with antiviral medications.

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.
## Guide 7
### Supportive care

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu</td>
<td>• Get the influenza vaccine every year but not the live, attenuated type.</td>
</tr>
<tr>
<td>Pneumococcal infection</td>
<td>• Get the pneumococcal polysaccharide vaccine every 5 years.</td>
</tr>
<tr>
<td>Shingles</td>
<td>• Get the recombinant, adjuvanted zoster vaccine before starting treatment or if on a BTK inhibitor.</td>
</tr>
</tbody>
</table>
| Frequent, severe infections of ears, sinuses, or lungs | • Take antimicrobials as needed (for example, antibiotics).  
  • If IgG is less than 500 mg/dL, get infusions of immunoglobulin into a vein or skin every month. |
| Herpes                                         | • Prevent with a drug like acyclovir.                                            |
| Pneumocystis jiroveci pneumonia                | • Prevent with drugs like sulfamethoxazole and trimethoprim.                   |
| Hepatitis B reactivation                       | • Prevent or treat with entecavir or other antivirals.                         |
| Cytomegalovirus reactivation                   | • Take ganciclovir if virus is present or rising.                              |
| Hepatitis C                                    | • Treat with direct-acting antiviral agents.                                   |
| Cancer                                         | • Get screened for new cancers as needed.                                      |
| Autoimmune cytopenia                           | • Treat with corticosteroids, rituximab, IVIG, cyclosporin A, splenectomy, eltrombopag, or romiplostim. |
| Tumor lysis syndrome                           | • Prevent with hydration, managing hyperuricemia, and taking allopurinol, febuxostat, or rasburicase. |
| Tumor flare reaction                           | • Prevent with steroids if lymph nodes are enlarged and treat with steroids and antihistamines. |
| Blood clot                                     | • Treat with aspirin if not on an anticoagulant.                               |
| Blood transfusion needed                       | • Transfusion should be done according to hospital standards; all blood products should be radiated. |
Cancer
People with CLL are at higher risk for other cancers, so it is important to get regular cancer screening. There are screening protocols for prostate, breast, cervical, lung, and colorectal cancers. People with CLL are also at risk for non-melanoma skin cancers. See a dermatologist once a year and protect your skin from the sun.

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

Tumor lysis syndrome
Some treatments for CLL kill many cells quickly.

- Chemoimmunotherapy
- Venetoclax
- Lenalidomide
- Obinutuzumab

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

Blood clots and tumor flare
Lenalidomide may cause blood clots and tumor flare. Symptoms of tumor flare include enlarged lymph nodes or spleen, low fever, and rash. There are medicines to prevent blood clots and tumor flare.

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.

Treatment response
A treatment response is the extent that the cancer improves. Treatment responses vary widely between people with CLL. To assess the treatment response, you will need to repeat some tests that you had before treatment.

- Complete remission is the best result. Enlarged organs and lymph nodes are back to normal size. You have no leukemia symptoms like fever. Blood counts are within normal range. No leukemia 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 are returning to normal.
- Stable disease is less than a partial remission. The cancer is not getting worse.
- Progressive disease is a worsening of the cancer.
Minimal residual disease
Minimal residual disease (MRD) is a very small number of leukemia cells in bone marrow or blood. There are so few leukemia cells that special tests are needed to detect them. MRD can be detected by 3 types of tests:

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

NGS-based assays are especially good at finding leukemia cells. They can find 1 leukemia cell within 1 million cells.

Undetectable MRD means the special tests detected no leukemia cells. There may be no leukemia cells or too few to be found. Despite these great results, CLL may not be cured.

Undetectable MRD may predict the results of treatment better than a complete response. Research supports the use of MRD testing to assess treatment response.

CLL in remission
When remission is achieved, your doctor will monitor the status of CLL. You will have regular visits with your treatment team. CLL tends to worsen over time, but it may take years before a second-line treatment is needed. The return of leukemia is called a relapse.

After achieving remission with BCR inhibitors, keep taking the treatment. Over time, the leukemia cells may mutate and develop resistance to treatment. Start a second-line treatment quickly when relapse occurs.

“Approach your ‘recovery’ in whatever way you deem best for your situation. Allow yourself to heal. Be positive and stay proactive.”

– Ted

“It is essential to have a doctor that you trust implicitly, and who knows that you are the ultimate decision-maker in your treatment regimen. If you can’t advocate for yourself, ask a family member or friend for help.”

– Dixie
People treated with chemoimmunotherapy or targeted therapy for a limited time may start “watch and wait.” Also called observation or watchful waiting, it is a period of testing to assess for changes in cancer status. Treatment may be started if signs of cancer appear.

Second-line treatment

If first-line treatment didn’t work, second-line treatment might. In this case, the goal is to try a different strategy than first-line treatment. When treatment doesn’t work the leukemia is described as refractory.

Second-line treatment is also an option if your cancer relapses. For a relapse, your doctor may give the same or a different treatment than was given before.

Your doctor will plan treatment based on multiple factors.

- Your overall health, medications, and preferences
- Previously known biomarkers
- New biomarkers, such as BTK and PLCG2 mutations, which may make BTK inhibitors not work
- First-line treatment and its side effects
- Type and duration of treatment response to first-line treatment

Clinical trial

A clinical trial may be an option. The best order of current treatments is being studied. There may be a clinical trial of a new treatment. Ask your treatment team if there is a clinical trial that is right for you.

Regimens

Preferred regimens include the BTK inhibitors ibritinib, acalabrutinib, and zanubrutinib. If a BTK inhibitor stopped working because of a mutation, a different one won’t work either.

Venetoclax regimens are a preferred treatment. They may be an option if BTK inhibitors stopped working because the CLL cells have mutated.

There is a wide range of other options. Like first-line treatments, options depend on 17p deletion and TP53 mutations. These biomarkers may change and become more common after first-line treatment. Second-line regimens are listed in Guide 8 and Guide 9.

Stem cell transplant

A hematopoietic stem cell is a cell in the bone marrow that develops into every type of blood cell. An allogeneic hematopoietic stem cell transplant forms new, healthy bone marrow that makes healthy blood cells. An allogeneic transplant uses healthy stem cells from a donor.

Your doctor may discuss allogeneic stem cell transplant with you. It may be an option if other treatments for CLL stop working well. For a transplant, you must not have major health problems other than the cancer.
### Guide 8
**Second-line regimens for CLL without 17p deletion and TP53 mutation**

<table>
<thead>
<tr>
<th>Preferred regimens</th>
<th>Other regimens for people who are 65 years of age and over or who have major health conditions</th>
<th>Other regimens for people who are under 65 years of age and fairly healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acalabrutinib</td>
<td>• Chlorambucil and rituximab</td>
<td>• Bendamustine and rituximab</td>
</tr>
<tr>
<td>• Ibrutinib</td>
<td>• Duvelisib</td>
<td>• Duvelisib</td>
</tr>
<tr>
<td></td>
<td>• Idelalisib with or without rituximab</td>
<td>• FCR</td>
</tr>
<tr>
<td></td>
<td>• Lenalidomide with or without rituximab</td>
<td>• Idelalisib with or without rituximab</td>
</tr>
<tr>
<td></td>
<td>• Obinutuzumab</td>
<td>• Lenalidomide with or without rituximab</td>
</tr>
</tbody>
</table>

- **Other regimens for people who are 65 years of age and over or who have major health conditions**:
  - Chlorambucil and rituximab
  - Duvelisib
  - Idelalisib with or without rituximab
  - Lenalidomide with or without rituximab
  - Obinutuzumab
  - Ofatumumab
  - Venetoclax
  - Bendamustine and rituximab
  - HDMP and either rituximab or obinutuzumab

- **Other regimens for people who are under 65 years of age and fairly healthy**:
  - Bendamustine and rituximab
  - Duvelisib
  - FCR
  - Idelalisib with or without rituximab
  - Lenalidomide with or without rituximab
  - Obinutuzumab
  - Ofatumumab
  - Venetoclax
  - HDMP and either rituximab or obinutuzumab

### Guide 9
**Second-line regimens for CLL with 17p deletion or TP53 mutation**

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<td>• Zanubrutinib</td>
<td>• Lenalidomide with or without rituximab</td>
</tr>
<tr>
<td>• Venetoclax and rituximab</td>
<td></td>
<td>• Ofatumumab</td>
</tr>
</tbody>
</table>

- **Other regimens**:
  - Alemtuzumab with or without rituximab
  - Duvelisib
  - HDMP and rituximab
  - Ofatumumab

- **Other regimens**:
  - Idelalisib with or without rituximab
  - Lenalidomide with or without rituximab
  - Ofatumumab
There are several steps to receiving an allogeneic transplant. You may stay on cytoreductive treatment to reduce spleen size and improve symptoms until you get a transplant.

**Step 1** – Your blood will be tested for cell proteins called human leukocyte antigens (HLAs). HLAs mark your cells so your body knows which cells are yours. A donor’s HLA type must be a near-perfect match to yours for a transplant to work. Otherwise, your body will reject the donor stem cells or the donor cells will attack your body. 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 healthy stem cells. It also weakens the immune system so your body does not kill the donor cells. Conditioning usually involves chemotherapy. Radiation therapy is sometimes used by itself or with chemotherapy.

**Step 3** – Next, you’ll receive the donor cells through a transfusion. A transfusion is a slow injection of blood products into a vein. The donor cells will travel to your bone marrow, nest there, and grow. They will also attack cancer cells that weren't killed by prior treatment. 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 stay in a very clean room at the hospital or be given antibiotics to prevent or treat infection. You may receive medicine called immunosuppressants to prevent GVHD. While waiting for the cells to engraft, you will likely feel tired and weak.

To learn more about GVHD, read the *NCCN Guidelines for Patients: Graft-Versus-Host Disease* at NCCN.org/patientguidelines.

### Richter’s transformation

A few people with CLL develop a faster-growing lymphoma. This change is called Richter’s transformation or Richter’s syndrome. The new lymphoma can evolve from mutations within CLL cells or from another B cell. Richter’s transformation can occur before or after treatment of CLL.

Testing is needed to confirm Richter’s transformation. A biopsy of lymph nodes will be done. The removed cells will be assessed for proteins on their surface. Blood tests and imaging will be done, too.

CLL most often changes into diffuse large B-cell lymphoma (DLBCL). Less often, it changes into Hodgkin lymphoma.
**DLBCL**

Treatment options depend on if the DLBCL cells evolved from CLL cells. If the cells are not related, the lymphoma is treated as DLBCL. To learn about treatment, see *NCCN Guidelines for Patients: Diffuse Large B-Cell Lymphoma* at NCCN.org/patientguidelines.

For DLBCL that evolved from CLL cells, a clinical trial is preferred. Another option is rituximab-based chemoimmunotherapy. If chemoimmunotherapy works, you may receive an allogeneic transplant if you are healthy enough.

If chemoimmunotherapy doesn’t work, there are 3 options. A clinical trial is preferred. Another option is a different treatment of DLBCL. The third option is immunotherapy with either nivolumab (Opdivo) or pembrolizumab (Keytruda). Ibrutinib may be received with immunotherapy. More research on immunotherapy for Richter’s transformation is needed.

**Hodgkin lymphoma**

A clinical trial is a preferred treatment option. Another option is treatments used for Hodgkin lymphoma. To learn about these treatments, see *NCCN Guidelines for Patients: Hodgkin Lymphoma* at NCCN.org/patientguidelines.

- Tests of biomarkers are needed before starting treatment. New biomarkers may appear during watch and wait or after first-line treatments.
- The preferred first-line treatment is a regimen with a BTK inhibitor or venetoclax. Other options may be chemoimmunotherapy or CD20 antibody treatment.
- The goal of treatment is to achieve a remission and stop CLL from growing.
- Supportive care is an important part of your cancer care. It can help prevent life-threatening infections.
- If first-line therapy doesn’t work, you may receive a different type of treatment. For a relapse, your doctor may give the same or a different treatment than was given before.
- CLL can transform into a faster-growing cancer. Clinical trials, chemotherapy, and immunotherapy may be options if this happens.
It’s important to be comfortable with the cancer treatment you choose. This choice starts with having an open and honest conversation with your doctors.

**It’s your choice**

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

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 decisions:

- What you want and how that might differ from what others want
- Your religious and spiritual beliefs
- Your feelings about certain treatments like chemotherapy or transplants
- Your feelings about pain or side effects such as nausea and vomiting
- Cost of treatment, travel to treatment centers, and time away from 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 doctor. If you take the time to build a relationship with your doctor, 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 can’t be ignored, there is time to have another doctor 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 doctors are listed on the following pages. Feel free to use these questions or come up with your own. Be clear about your goals for treatment and find out what to expect from treatment.
Questions to ask about testing and staging

1. What tests will I have?
2. Do I need a biopsy? What kind of biopsy do I need? What are the risks?
3. How do I prepare for testing?
4. What if I am pregnant?
5. Where do I go to get tested? How long will the tests take and will any test hurt?
6. Should I bring someone with me? Should I bring a list of my medications?
7. How soon will I know the results and who will explain them to me?
8. Would you give me a copy of the pathology report and other test results?
9. What type of leukemia do I have? Is this a fast- or slow-growing leukemia?
10. What is the Rai stage? Does this stage mean the leukemia is advanced?
11. Can this cancer be cured? If not, how well can treatment stop the cancer from growing?
12. Who will talk with me about the next steps? When?
Questions to ask about treatment options

1. What are my treatment options? Are you suggesting options other than what NCCN recommends? If yes, why?

2. Do your suggested options include clinical trials? Please explain why.

3. What will happen if I do nothing?

4. How do my age, overall health, and other factors affect my options? What if I am pregnant or planning to get pregnant?

5. Does any option offer a cure or long-term cancer control? Are my chances any better for one option than another? Less time-consuming? Less expensive?

6. How do you know if treatment is working? How will I know if treatment is working?

7. What are my options if treatment stops working?

8. What are the possible complications? What are the short- and long-term side effects of treatment?

9. What can be done to prevent or relieve the side effects of treatment?

10. What supportive care services are available to me during and after treatment?

11. Can I stop treatment at any time? What will happen if I stop treatment?
Questions to ask about clinical trials

1. Are there clinical trials for my type of cancer?

2. What are the treatments used in the clinical trial?

3. What does the treatment do?

4. Has the treatment been used before? Has it been used for other types of cancer?

5. What are the risks and benefits of this treatment?

6. What side effects should I expect? How will the side effects be controlled?

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 the treatment is working?

10. Will the clinical trial cost me anything? If so, how much?
Questions to ask about getting treated

1. Will I have to go to the hospital or elsewhere? How often? How long is each visit?

2. What do I need to think about if I will travel for treatment?

3. Do I have a choice of when to begin treatment? Can I choose the days and times of treatment?

4. How do I prepare for treatment? Do I have to stop taking any of my medicines? Are there foods I will have to avoid?

5. Should I bring someone with me when I get treated?

6. Will the treatment hurt?

7. How much will the treatment cost me? What does my insurance cover?

8. Will I miss work or school? Will I be able to drive?

9. Is home care after treatment needed? If yes, what type?

10. How soon will I be able to manage my own health?

11. When will I be able to return to my normal activities?
Resources

Aplastic Anemia and MDS International Foundation (AAMDS)
aamds.org

CLL Society
CLLSociety.org

Leukemia & Lymphoma Society
LLS.org/PatientSupport

Lymphoma Research Foundation
lymphoma.org/aboutlymphoma/cll

NCCN Patient Resources
NCCN.org/patients

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
Words to know

**alkylating agent**  
A drug that damages a cell’s DNA by adding a chemical to it.

**ALL**  
acute lymphoblastic leukemia

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

**AML**  
acute myeloid leukemia

**anemia**  
A health condition in which 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 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.

**BCR**  
B cell receptor

**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

**CML**  
chronic myeloid 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.
Words to know

**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.

**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.

**ECOG**
Eastern Cooperative Oncology Group

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

**FCR**
Fludarabine, cyclophosphamide, and rituximab

**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

**haptoglobin**
One of the proteins made by the liver.

**HDMP**
high-dose methylprednisolone

**hemoglobin**
A protein with iron in red blood cells.

**hemolysis**
The early death of red blood cells.

**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 cell markers involved in abnormal cell growth.

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

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

**kinase inhibitor**
A drug that blocks cell signals for cell growth.

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

**lymph**
A clear fluid containing white blood cells.

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

**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.

**mantle cell lymphoma**
A cancer of B cells that have too many proteins called cyclin D1.

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

**monoclonal antibody**
A type of cancer drug that stops growth signals.

**MRD**
minimal residual disease

**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 while not receiving treatment.

**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.

**purine analogs**
A drug that prevents the DNA “building blocks” labeled A and G from being used.

**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.
Words to know

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.

steroid
A drug used to reduce redness, swelling, and pain, but also to kill cancer cells.

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

targeted therapy
A drug treatment that impedes the growth process specific to cancer cells.

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

ultrasound
A test that uses sound waves to take pictures of the inside of the body. Also called ultrasonography.

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.
This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 2.2022 – January 18, 2022. It was adapted, reviewed, and published with help from the following people:

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Chronic Lymphocytic Leukemia, 2022

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507.538.3270 • Minnesota
mayo.clinic.org/cancercenter

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New York, New York
800.525.2225 • mskcc.org

Moffitt Cancer Center
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888.663.3488 • moffitt.org

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866.587.4322 • cancer.northwestern.edu

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877.277.7724 • roswellpark.org

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800.600.3606 • siteman.wustl.edu

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