

Understanding Lymphoma and Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL/SLL)



Part 4 — Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Chapter 16: What is CLL/SLL?

What is CLL/SLL?

Until the 1990s, doctors believed that chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) were two different diseases. However, recent research has shown that CLL and SLL are actually the same disease. If the cancer cells are found mainly in the lymph nodes, the disease is called SLL. If high levels of cancer cells are found in the bloodstream, then the disease is typically called CLL. Cancer cells are often found in both the lymph nodes and the bone marrow (the spongy tissue inside the bones) of patients with SLL and CLL, and patients with CLL can also have enlarged lymph nodes at the time of diagnosis. Over time, a patient with *relapsed* (disease returns after treatment) CLL may develop enlarged lymph nodes like a patient with SLL, and a patient with relapsed SLL may have cancer cells in the blood like a patient with CLL. In fact, most cases of SLL become CLL over time. Because they are essentially the same disease presenting in different parts of the body, the two terms are now grouped together as a single condition known as “CLL/SLL”. Since patients with CLL and SLL receive the same treatments and the prognosis is similar, the rest of this guide will use the term CLL/SLL, unless a distinction needs to be made between the two conditions.

Although CLL is a leukemia, CLL and SLL are in the family of B-cell lymphomas within the larger category of non-Hodgkin lymphoma (NHL). Doctors consider CLL/SLL to be an *indolent* (slow-growing) type of lymphoma because it may remain inactive (with no symptoms) over an extended period of time and can be managed like a chronic disease (long-lasting medical condition that can be controlled but not cured).

Occasionally, CLL/SLL may progress or transform to a more aggressive (fast-growing) type of lymphoma. This transformation from CLL/SLL to a more aggressive lymphoma (usually diffuse large B-cell lymphoma) is called Richter syndrome or Richter transformation.

How Common is CLL/SLL?

About 19% of patients with a B-cell lymphoma have CLL/SLL, making it the third most common type of B-cell lymphoma. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, approximately 18,740 people in the United States are diagnosed with CLL/SLL each year. In 2020, there were approximately 207,463 people living with CLL in the US. This disease is rare in people younger than 40 years. The median age at diagnosis is 70.

What Causes CLL/SLL?

The exact cause of CLL/SLL is not known. Like other types of indolent lymphoma, CLL/SLL develops over a long time after lymphocytes accumulate genetic changes (called *mutations* and *chromosomal abnormalities*) that may cause them to grow abnormally. Some of these mutations make the abnormal lymphocytes divide faster and/or live longer than normal lymphocytes.

These abnormal cells accumulate in the lymph nodes, bone marrow, bloodstream, and other organs. The increasing numbers of cancer cells in the blood and bone marrow crowd out healthy white blood cells, red blood cells, and platelets. Patients with CLL/SLL also have low levels of antibodies that fight infections (called *immunoglobulins*). Because of all these changes, patients with CLL/SLL are more likely to have infections, low levels of red blood cells in the blood (anemia), and/or low platelet counts (thrombocytopenia), causing them to have an increased risk of bleeding more easily.

Just like healthy cells, cancerous lymphocytes can travel through the lymphatic system. This ability to move around lets them spread and grow in many parts of the body. This is why CLL/SLL and most other types of indolent NHL are already found throughout the body by the time a patient is diagnosed with the disease. This is typical and is not an indication of a delay in diagnosis.

Why Do Some People Develop CLL/SLL?

The reasons why certain people develop CLL/SLL are not totally understood. However, scientists have found that people with particular

characteristics, called *risk factors*, have a slightly higher chance of developing CLL/SLL. Having one or more risk factors for CLL/SLL does not mean a person will develop the disease. In fact, most people with the known risk factors never develop CLL/SLL, and many people diagnosed with CLL/SLL do not have any of these risk factors. However, there does seem to be a correlation between the risk factors described below and the development of CLL/SLL.

Known risk factors for CLL/SLL include:

- Increasing age
- Male sex
- Having a first-degree relative (parent, sibling, or child) with CLL/SLL
- Having European ancestry
- Being exposed to Agent Orange (an herbicide used during the Vietnam war) and excessive, long term exposure to some pesticides used in farming. Veterans who have CLL/SLL and were exposed to Agent Orange can contact their local Veterans Affairs office to ask about benefits that may be available.
- Having a diagnosis of monoclonal B-cell lymphocytosis (MBL), a condition characterized by higher than normal levels of lymphocytes, but not high enough to classify as CLL. There is a small risk that these patients may develop CLL in the future (about 1% for each year of MBL diagnosis).

CLL/SLL cannot be caused by injury and cannot be caught from someone who has the disease. CLL/SLL is rarely caused by inherited mutations.

What Are the Signs and Symptoms of CLL/SLL?

Approximately 50-75% of patients with CLL/SLL do not have any obvious signs or symptoms of the disease at the time of diagnosis. Their doctors might detect the disease during routine blood tests and/or a physical examination. Besides a higher than normal number of white blood cells, the immune system of people with CLL may also produce antibodies against their own red blood cells and/or platelets (*autoantibodies*, your immune system mistakes your red blood cells and platelets for foreign cells). For

others, CLL/SLL is discovered when symptoms occur and they go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 16.1, CLL/SLL may cause different signs and symptoms depending on the location of the tumor in the body. Keep in mind that many of these signs and symptoms are not specific to CLL/SLL or other types of NHL and may be due to other conditions.

Table 16.1. Signs and Symptoms Commonly Found in Patients With CLL/SLL

Sign or Symptom	Possible Reason
Shortness of breath, <i>fatigue</i> (extreme tiredness), and pale skin	Low red blood cell counts (<i>anemia</i>)
Severe or frequent infections	Reduced ability to fight infection due to low white blood cell counts or a reduced ability to make antibodies that fight infections (<i>hypogammaglobulinemia</i>)
Frequent nosebleeds, bleeding from the gums, tiny red marks on the skin caused by minor bleeding under the skin (<i>petechiae</i>), and bruising easily	Low platelet counts (<i>thrombocytopenia</i>)
“B symptoms” including fever for no known reason, unexplained drastic weight loss, or drenching night sweats that soak clothing and sheets. Patients may also experience chills.	Increased levels of inflammatory chemicals (substances that cause redness, swelling and pain) in the blood that are released by cancer cells or by the immune system
Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin	Lymph nodes, or “glands,” that swell because of an increased number of abnormal lymphocytes

When Should a Patient Seek Medical Attention?

Anyone who has an enlarged lymph node in the absence of an infection that does not return to normal size within a few weeks and/or persistent symptoms should see a doctor to make sure that CLL/SLL or another serious condition is not present. A good rule of thumb is to seek medical attention if any of the signs or symptoms listed in Table 16.1 last longer than 2 weeks, or sooner if the symptoms are intense enough to impact a person’s daily life. It is important to note that most patients with these

symptoms do not have CLL/SLL, as other diseases or conditions may cause many of these symptoms.

What Does the Doctor Look For During the Visit?

During their visit, patients should describe all symptoms to the doctor. The doctor will ask questions about their medical history and perform a complete physical examination, during which the doctor is likely to:

- Ask details about symptoms including duration (how long), frequency (how often), intensity (how severe), and pain; these can be tracked in a mobile device app such as the Lymphoma Research Foundation's mobile app, *Focus On Lymphoma*. This app can keep track of symptoms and make communications with your doctor easier and more accurate.
- Measure blood pressure and pulse
- Listen to the heart and lungs
- Check the throat for enlarged tonsils
- Look for any physical signs of infection or any other cancers, especially on the skin
- Check for swollen lymph nodes under the chin, in the neck and tonsil area, above the shoulders, on the elbows, in the underarms, and in the groin
- Examine other parts of the body to look for swelling or fluid that may be caused by swollen lymph nodes
- Examine the abdomen to see whether the liver and/or spleen are enlarged and to feel for masses
- Look for any weakness or paralysis that may be caused by an enlarged lymph node pressing against nerves

If the doctor suspects CLL/SLL, they will order tests to confirm the diagnosis. For CLL, it may be best to consult with a hematologist oncologist, a doctor who specializes in diagnosing and treating blood cancers.

These tests should include a complete blood count, a comprehensive metabolic panel (a group of 14 tests that measure different substances in blood) and assessing the performance status (ability to carry out day to day activities through a scoring system). Specific laboratory tests and

imaging tests (including scans) may also be required. A lymph node biopsy (a procedure that collects a small sample of the affected lymph node) may be needed for patients with suspected SLL. Doctors do not always need a bone marrow (the spongy tissue inside the bones) test to make the CLL/SLL diagnosis, but they may find it useful prior to treatment and/or to assess the response to therapy. These tests and procedures will be further discussed in more detail in this chapter.

How Is CLL/SLL Diagnosed?

CLL/SLL is diagnosed by testing the blood. Rarely are a bone marrow biopsy, or a lymph node biopsy necessary. Typically, once the diagnosis is made, there is no need to confirm it from additional sites. Most cases of CLL/SLL are diagnosed based on abnormal blood test results in people who do not have any symptoms of the disease. The doctor might also suspect that a patient has CLL/SLL because of reported symptoms or results of the physical examination. The following tests are usually used to confirm the diagnosis:

- Complete blood count with differential, a test in which the number of the different blood cells are measured. The diagnosis of CLL is characterized by a high white blood cell counts, and sometimes low levels of red blood cell and platelet counts
- Hematopathologic examination of blood smears and sometimes of a bone marrow biopsy
- Immunophenotyping by flow cytometry of the lymphocytes in the blood and lymph nodes. In these tests, chemicals or dyes are used to understand if certain proteins on the outside of the cell (*cell surface proteins*) are present. This information distinguishes CLL from other types of leukemia. Classic markers found in CLL/SLL include CD5, CD19, CD23 and dimCD20. To learn more about immunophenotyping, see Table 3.2 in Chapter 3 in Part 1 of this guide (page 16).
- Histopathologic examination of a lymph node biopsy (needed for diagnosis of SLL if flow cytometry from the blood does not provide enough information).

Patients diagnosed with a complicated disease like CLL/SLL will be asked to undergo a variety of procedures before treatment begins, during the course of treatment, and during the follow up period.

The doctor might also order one or more additional tests such as:

- Genetic tests (like *Fluorescence in situ hybridization* [FISH] or cytogenetic analyses) to look for acquired changes in specific regions of the chromosomes (thread-like structures that contain the genetic material). To learn more about FISH and cytogenetic analysis, see Table 3.3 in Chapter 3 in Part 1 of this guide (page 20).
- Molecular analysis to check on the mutation status of the immunoglobulin heavy chain variable region (*IGHV*) gene. Patients who have mutations in the *IGHV* gene usually do better than patients who do not have these mutations.
- Sequencing (determining the order of *nucleotides*, a component of DNA) of the TP53 gene to see if it contains mutations (changes)
- Blood levels of a protein called Beta-2 microglobulin
- Other tests that the doctor may deem to be useful for determining therapy

Prognostic Factors for CLL/SLL

Prognosis is the medical term for predicting how a patient will ultimately do with their disease.

The characteristics that help predict a patient's prognosis are called *prognostic factors*. Favorable or good prognostic factors tend to be associated with better outcomes (overall longevity or good response to any treatment), while unfavorable or poor prognostic factors tend to be associated with worse outcomes. Scientists have known about several prognostic factors, called traditional (most commonly used) prognostic factors, for many years or even decades, while novel (new) prognostic factors have only been recently identified (Table 16.2).

Table 16.2. Known Prognostic Factors for CLL/SLL

Traditional Prognostic Factors	Modern Prognostic Factors
<ul style="list-style-type: none">■ Rai stage■ Sex■ Age■ Beta-2 microglobulin levels in the blood	<ul style="list-style-type: none">■ FISH■ Immunoglobulin heavy chain variable (<i>IGHV</i>) gene mutation status■ <i>TP53</i> mutation

There are well over 100 different prognostic markers identified for patients with CLL/SLL. These prognostic markers are studied as independent predictors of outcome, meaning they look at only those who do and do not have the marker. Each prognostic marker will have a different amount of impact upon prognosis, i.e. some will override others.

FISH

FISH (Fluorescence in situ Hybridization) is a way to study the chromosomes inside CLL cells. Chromosomes contain genes that are made of very long strands of DNA (genetic material). Normal human cells have 23 pairs of chromosomes. CLL cells from some patients have a normal number of chromosomes, but some have too many or too few chromosomes, or they may have abnormal chromosomes that have undergone a genetic change. These changes can cause CLL cells to multiply. The most common types of chromosome abnormalities that occur in CLL/SLL are described below and in Table 16.3.

- *Deletion*: A common chromosomal abnormality in CLL/SLL is called a *deletion*, which happens when part of a chromosome is missing. The most common deletions, abbreviated as “del,” in CLL/SLL are seen in chromosomes 11, 13, and 17. Deletions in these chromosomes are written as del(11q), del(13q), and del(17p) in a patient’s FISH or karyotype testing report. Some patients’ cancer cells might have no detectable deletions at first, but they can develop deletions in chromosome 17 over time (called *clonal evolution*). Of all the prognostic markers (markers that indicate how well the patient will do), the most important to know is whether deletions in chromosome 17 are present, as this affects treatment selection.

- **Trisomy:** Another type of chromosomal abnormality that may be present in the DNA of CLL/SLL lymphocytes is trisomy, which indicates the presence of an extra copy of a chromosome. Normally there are two pairs of each chromosome, but if a mistake occurs during cell division, a third copy of the chromosome can be created.

Table 16.3. Chromosomal Changes and Genetic Mutations Most Commonly Found in CLL/SLL

Chromosome or Gene Mutation	Prevalence in Patients With CLL/SLL ^a
Del(13q14)	50% to 60%
Trisomy 12	10% to 20%
Del(11q23)	15% to 20%
Del(17p)	5% to 10%

Del means deletion of some of the genetic material. The numbers in parentheses (for example, 11q23) indicate the chromosome and the area on the chromosome where the deletion is located.

^aAt the time of diagnosis; over time, there may be clonal expansion and the percentage increases.

IGHV (Immunoglobulin Heavy Chain Variable)

To assess IGHV (Immunoglobulin Heavy Chain Variable) status, pathologists sequence (determine the order of the building-blocks that form the genetic material) the DNA inside the CLL cells to determine how similar the DNA in these cells is to the other cells in the body. If the DNA is very similar (2% or less difference) that is called “unmutated IGHV”, and if the DNA is less similar (>2% difference) that is called “mutated”. CLL cells from patients with unmutated IGHV CLL typically grow faster, so patients with this type of CLL often need treatment sooner. Patients with mutated IGHV CLL tend to have slower growing CLL which often takes longer before treatment is needed. Historically, chemotherapy-based regimens were not as effective for patients with unmutated IGHV, leading to shorter survival. Fortunately, the targeted therapies developed for CLL over the last decade are highly effective for patients with unmutated IGHV, so the prognosis for these patients has improved dramatically in recent years.

TP53 Mutations

Mutations in the TP53 gene (located on chromosome 17) can also be found in CLL. TP53 provides instructions for the cells to produce a tumor suppressor protein (a protein that controls cell division and causes the

death of cancer cells) called p53. In CLL, mutations in the TP53 have historically been associated with a poor prognosis. Note that to assess TP53 mutation status (the number and type of permanent changes in the TP53 gene), a separate blood test must be sent from the FISH test, as DNA sequencing (determining the order of building-blocks that form DNA) is required. This can be confusing, because some FISH results will report deletion TP53, but this is not the same thing as *TP53* mutation. Often, both del(17p) and *TP53* mutation are both present, but about 5% of patients with CLL will have *TP53* mutation alone at diagnosis. As with unmutated IGHV, the prognosis for patients with *TP53* mutation has improved dramatically in the last few years with the use of targeted therapies.

In summary, given the complexity of these molecular tests and their impact on prognosis, it is important for patients to discuss the interpretation of diagnostic tests with their doctor. Some important considerations when interpreting diagnostic tests are listed below.

Additionally, two important features of prognostic markers to remember are:

- What the prognostic marker is predicting. If the prediction is for time to treatment, but everyone does equally well with treatment, then the prognostic marker becomes less important in terms of understanding how long patients will survive with the disease.
- They are only helpful in the setting in which they were studied. For example, IGHV mutated CLL/SLL patients have longer responses to chemoimmunotherapy than those with unmutated IGHV. But both do equally well in response to targeted therapy with Bruton's tyrosine kinase (BTK) inhibitors and therefore, IGHV is no longer a prognostic marker for response to BTK inhibitors.

Cautions About Interpreting Diagnostic Reports

- If patients wish to look at their written or electronic test reports, it is important for them to review and interpret the findings carefully with their doctor
- Some test results may be reported as "normal" even though CLL/SLL is present

- Some test results may be reported as “abnormal” even though CLL/SLL is not present
- Other conditions can produce signs and symptoms similar to CLL/SLL
- The interpretation of test results, such as imaging studies and scans, can be lengthy, complex, and difficult in some situations
- Follow-up tests are often needed to determine the significance of previous results, and additional biopsies may be needed to clarify the results

Part 4 — Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chapter 17: Treatment of CLL/SLL

This chapter reviews the most common therapies currently used in the treatment of CLL/SLL. Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was published. See Chapter 17 to learn more about emerging treatments under investigation.

There are important differences in the cancer cells found in different patients with CLL/SLL. Because of these differences, a treatment that may work very well in one patient may not have the same positive effect in another.

What Types of Treatments Are Used in Patients With CLL/SLL?

There are 3 general types of treatments approved for patients with CLL/SLL:

- *Active surveillance* (observation with no treatment), in which the patient is closely monitored to see if/when treatment should be started.
- Drug therapy, including one or more of the following types of drugs:
 - Targeted therapies, which affect special characteristics or internal workings of CLL cells
 - Immunotherapy, which helps the body's immune system attack CLL cells
 - Chemotherapy, which affects general cell growth and proliferation (the ability of cells to multiply). It is important to add that chemotherapy currently plays a very limited role in the treatment of CLL/SLL.
- Stem cell transplantation, which replaces the patient's immune system with healthy immune cells.

Each of these types of therapies is described in detail in this chapter.

What Is Active Surveillance?

With the active surveillance (or *watchful waiting*) approach, patients' health and disease are monitored through regular checkups and evaluation procedures, such as laboratory and imaging tests, but they do not receive any CLL treatments. These patients continue to remain untreated as long as they do not show any signs or symptoms and there is no evidence that the CLL is growing or spreading. If the lymphocyte counts doubles in less than 6 months, this can be a sign that the CLL is becoming more active, but in and of itself does not lead to a need for CLL treatment.

Doctors use established criteria to help determine when the disease is becoming more active and the patient should no longer remain on active surveillance. These criteria include:

- Progressive bone marrow failure; indicated by anemia (low levels of red blood cells; Rai stage III) or thrombocytopenia (low platelet levels; Rai stage IV). To learn more about Rai staging for CLL/SLL, see Chapter 5 in Part 1 of this guide (page 33).
- Development of large (bulky) lymph nodes
- Enlargement of the spleen (splenomegaly)
- Autoimmune cytopenias (body attacks its own blood cells) that is not resolved by treatment with steroids
- B symptoms (fever and/or chills for no known reason, unexplained weight loss, and drenching night sweats that soak clothing and sheets)
- Severe fatigue (extreme tiredness) due to progressing CLL/SLL
- A threat caused by the CLL to one or more organs

Though doctors may recommend active surveillance for selected patients with *indolent* CLL/SLL, it is not a treatment option for patients with advanced CLL/SLL (when CLL cells outnumber the healthy cells in the bone marrow and the disease becomes more severe). While the decision to start treatment depends on the clinical judgment of the treating physician, treatment for patients with advanced CLL/SLL should generally start soon after patients reach this stage. For more information about active surveillance see Chapter 7 in Part 1 of this guide (page 52).

What Drugs Are Used to Treat CLL/SLL?

Patients with CLL/SLL are commonly given either a single drug or a combination of drugs. The purpose of combining drugs is to increase how effectively they damage or kill cancer cells, to diminish the chances of the cancer cells becoming resistant to treatment, or to allow lower doses of each drug to be used to minimize side effects. Some patients receive treatment in cycles at specific intervals (followed by rest periods), and other patients may be treated daily for an indefinite amount of time (for some oral drugs like pills, tablets or capsules).

Drugs may be combined to create a *treatment regimen*—a specific schedule that determines which drugs are given in which doses on which days of each treatment cycle.

Treatment regimens for CLL/SLL may include chemotherapy, immunotherapy, and/or targeted therapy. Most chemotherapy and monoclonal antibody drugs used to treat CLL/SLL are given intravenously (as a liquid that is infused directly into a vein, commonly known as an “IV”). Table 17.1 lists the drug regimens currently FDA approved for the treatment of CLL/SLL. This list is subject to change as the FDA approves new CLL/SLL treatments.

Table 17.1. Drug regimens currently FDA approved for the treatment of CLL/SLL

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)	Delivery Method
Acalabrutinib alone	Acalabrutinib (Calquence)	Oral capsules
Acalabrutinib plus obinutuzumab	Acalabrutinib (Calquence) Obinutuzumab (Gazyva)	Oral capsules IV infusion
Alemtuzumab ^a alone	Alemtuzumab (Campath)	IV infusion
Alemtuzumab ^a with rituximab	Alemtuzumab (Campath) Rituximab (Rituxan)	IV infusion IV infusion
Bendamustine plus obinutuzumab	Bendamustine (Bendeka, Treanda) Obinutuzumab (Gazyva)	IV infusion IV infusion
Bendamustine plus ofatumumab ^b	Bendamustine (Bendeka, Treanda) Ofatumumab (Arzerra)	IV infusion IV infusion

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)	Delivery Method
Bendamustine plus rituximab	Bendamustine (Bendeka, Treanda) Rituximab (Rituxan)	IV infusion IV infusion
BR plus ibrutinib	Bendamustine (Bendeka, Treanda) Rituximab (Rituxan) Ibrutinib (Imbruvica)	IV infusion IV infusion Oral capsules/tablets/oral suspension
Chlorambucil plus obinutuzumab	Chlorambucil (Leukeran) Obinutuzumab (Gazyva)	Oral tablets IV infusion
Chlorambucil plus ofatumumab ^b	Chlorambucil (Leukeran) Ofatumumab (Arzerra)	Oral tablets IV infusion
Chlorambucil plus rituximab	Chlorambucil (Leukeran) Rituximab (Rituxan)	Oral tablets IV infusion
Duvelisib	Duvelisib (Copiktra)	Oral capsules
FC plus ofatumumab ^b	Fludarabine (Fludara) Cyclophosphamide (Cytoxan) Ofatumumab (Arzerra)	IV infusion Oral tablets or IV infusion IV infusion
FCR	Fludarabine (Fludara) Cyclophosphamide (Cytoxan) Rituximab (Rituxan) or Rituximab hyaluronidase (Rituxan Hycela)	IV infusion Oral tablets or IV infusion IV infusion or SC injection
FR	Fludarabine (Fludara) Rituximab (Rituxan)	IV infusion IV infusion
HDMP-R	High-dose methylprednisolone (Solu-Medrol and others) Rituximab (Rituxan)	IV infusion or intramuscular (IM) injection IV infusion
Ibrutinib alone	Ibrutinib (Imbruvica)	Oral capsules/tablets/oral suspension
Ibrutinib plus obinutuzumab	Ibrutinib (Imbruvica) Obinutuzumab (Gazyva)	Oral capsules/tablets/oral suspension IV infusion

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)	Delivery Method
Ibrutinib plus rituximab	Ibrutinib (Imbruvica)	Oral capsules/tablets/oral suspension
	Rituximab (Rituxan)	IV infusion
Idelalisib alone	Idelalisib (Zydelig)	Oral tablets
Idelalisib plus rituximab	Idelalisib (Zydelig)	Oral tablets
	Rituximab (Rituxan)	IV infusion
Lenalidomide alone	Lenalidomide (Revlimid)	Oral capsules
Lenalidomide plus rituximab	Lenalidomide (Revlimid)	Oral capsules
	Rituximab (Rituxan)	IV infusion
Obinutuzumab alone	Obinutuzumab (Gazyva)	IV infusion
Ofatumumab ^b alone	Ofatumumab (Arzerra)	IV infusion
Rituximab alone	Rituximab (Rituxan)	IV infusion
	Rituximab-abbs ^c (Truxima)	IV infusion
Rituximab and hyaluronidase human ^d	Rituximab and hyaluronidase human (Rituxan Hycela)	SC injection
Venetoclax alone	Venetoclax (Venclexta)	Oral tablets
Venetoclax plus obinutuzumab	Venetoclax (Venclexta)	Oral tablets
	Obinutuzumab (Gazyva)	IV infusion
Venetoclax plus rituximab	Venetoclax (Venclexta)	Oral tablets
	Rituximab (Rituxan)	IV infusion
Zanubrutinib alone	Zanubrutinib (Brukinsa)	Oral capsules

^aAlemtuzumab is provided only through the Campath Distribution Program; it is no longer commercially available.

^bOfatumumab is provided only through the Arzerra Oncology Access Program; it is no longer commercially available.

^cRituximab-abbs is a biosimilar and may or may not be interchangeable. Patients are encouraged to talk to their physician about the option to use a biosimilar for treatment.

^dOne full dose of rituximab must be dosed by IV infusion before a patient may be eligible for rituximab hyaluronidase subcutaneous injection.

IV, intravenous; SC, subcutaneous.

Immunotherapy

The term immunotherapy refers to treatments that use the body's own immune response to fight cancer (see Chapter 6 in Part 1 of this guide). There are many different types of immunotherapy, but only a specific type called monoclonal antibodies are approved to treat patients with CLL/SLL. The three monoclonal antibodies that are approved to treat CLL are described below.

For more information, read the sections below about types of immunotherapy and see the *Immunotherapy and Other Targeted Therapies* fact sheet on LRF's website at lymphoma.org/publications.

Monoclonal Antibodies

Monoclonal antibodies are molecules that have been engineered in a laboratory to attach to one specific target (antigen). This target is specifically chosen to be useful for the treatment of the cancer. Antibodies generated in the laboratory are all identical in their protein sequence (order of the building blocks that form proteins). Once injected in the patient, the monoclonal antibodies travel through the blood and attach themselves to the cells that have antigens they recognize, most of which are CLL/SLL cells. This can either stop or slow down the growth of the cancer cell, or it can trigger an "alarm" that makes it easier for other cells in the immune system to recognize and destroy the cancer cell.

The monoclonal antibody therapies used to treat CLL/SLL are given as IV infusions or subcutaneous (under the skin) injections. Two monoclonal antibodies are used in the treatment of CLL/SLL: rituximab (Rituxan) and obinutuzumab (Gazyva). Alemtuzumab (Campath) and ofatumumab (Arzerra) are no longer commercially available but can be obtained for clinical use. Alemtuzumab is provided only through the Campath Distribution Program, while ofatumumab (Arzerra) is provided only through the Arzerra Oncology Access Program. With the exception of alemtuzumab (Campath), these treatments are directed against different parts of CD20, an antigen that is almost universally present on the surface of B-cells, including the malignant lymphocytes in CLL/SLL. Because they target different parts of CD20, each of these drugs work a bit differently.

Obinutuzumab (Gazyva)

Obinutuzumab (Gazyva) is approved by the FDA for the treatment of patients with previously untreated CLL in combination with chlorambucil (Leukeran). It may also be used in combination with venetoclax (Venclexta), ibrutinib (Imbruvica) or acalabrutinib (Calquence).

Patients usually receive the first dose split over two days during the first week, followed by one dose a week for two weeks (this is the first cycle of therapy), then once every 28 days for five more cycles.

Rituximab (Rituxan) and Rituximab Plus Hyaluronidase Human (Rituxan Hycela)

In 1997, rituximab (Rituxan) became the first monoclonal antibody approved by the FDA for the treatment of patients with lymphoma. Rituximab is approved by the FDA for the treatment of adult patients with previously untreated or treated CD20-positive CLL/SLL in combination with FC chemotherapy (fludarabine and cyclophosphamide).

The original form of rituximab (Rituxan) is given as an IV infusion, and the treatment regimen varies depending on the combination of drugs used. When combined with chemotherapy, rituximab is usually given during the first day of each chemotherapy cycle.

A subcutaneous formulation of rituximab (Rituxan Hycela or “rituximab and hyaluronidase human”) was approved by the FDA in 2017 for use in patients with previously untreated or treated CLL in combination with FC (fludarabine and cyclophosphamide) chemotherapy. Subcutaneous administration allows the drug to be given in a shorter period of time. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must first have at least one full dose of IV rituximab.

Targeted Therapies

This term refers to drugs that target molecules that cancer cells use to survive, multiply, and spread in the body. To learn more about targeted therapies, please view Chapter 7 of this guide (page 57).

FDA approved targeted therapies used in the treatment of CLL/SLL include:

- The Bruton tyrosine kinase (BTK) inhibitors ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa), and pirtobrutinib (Jaypirca). These drugs inhibit the signaling protein BTK to block the growth and survival of cancer cells.
- The phosphatidylinositol 3-kinase (PI3K) inhibitor idelalisib (Zydelig) and duvelisib (Copiktra). These drugs block the signaling protein PI3K to block the growth and cause the death of cancer cells.
- The B-cell lymphoma 2 (Bcl2) inhibitor venetoclax (Venclexta). This drug targets the Bcl2 protein, which is essential for cancer cell survival.

Ibrutinib (Imbruvica)

Ibrutinib (Imbruvica) is approved for treatment of adult patients with CLL/SLL, with or without del(17p). It can be used as single agent or in combination with other drugs approved for the treatment of CLL/SLL (See Table 17.1). Ibrutinib (Imbruvica) comes in the form of capsules, tablets or oral suspension taken orally once a day. Capsules and tablets must be swallowed whole.

Acalabrutinib (Calquence)

Acalabrutinib (Calquence) is approved for treatment of adult patients with CLL/SLL. It can be used in monotherapy or in combination with obinutuzumab (Gazyva). Acalabrutinib (Calquence) is taken orally twice a day and comes in a tablet form that should be swallowed whole.

Zanubrutinib (Brukinsa)

Zanubrutinib (Brukinsa) is approved as monotherapy for treatment of adult patients with CLL/SLL. Zanubrutinib (Brukinsa) is taken orally twice a day, or once a day, and comes in the form of capsules that should be swallowed whole.

Pirtobrutinib (Jaypirca)

Pirtobrutinib (Jaypirca) is indicated for the treatment of adult patients with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a Bcl-2 inhibitor. It is taken as an oral tablet once a day with water.

Idelalisib (Zydelig)

Idelalisib (Zydelig) is approved in combination with rituximab, for the treatment of patients with CLL for whom rituximab alone would be considered appropriate therapy due to other co-morbidities (other diseases or medical conditions of the patient).

Idelalisib may only be used in patients who have received other lymphoma treatments; it is not intended to be used as frontline (initial) therapy. Idelalisib (Zydelig) is taken orally twice a day and comes in the form of tablets that should be swallowed whole.

Duvelisib (Copiktra)

Duvelisib (Copiktra) is approved for the treatment of adult patients with relapsed or refractory CLL/SLL after at least two prior therapies. Duvelisib (Copiktra) is taken orally twice a day and comes in the form of capsules that should be swallowed whole.

Venetoclax (Venclexta)

Venetoclax (Venclexta) is approved as monotherapy or in combination with obinutuzumab (Gazyva) for the frontline treatment of adult patients with CLL/SLL. It is also approved in combination with rituximab (Rituxan) in the treatment of patients with previously treated CLL/SLL which has relapsed or become refractory. Venetoclax (Venclexta) is taken orally once daily and comes in the form of tablets that must be swallowed whole. Venetoclax is typically given in a *ramp up schedule* (doses are gradually increased over the course of 4 weeks) until the ideal dose is attained. You will need your labs monitored around the dose ramp-up of venetoclax to monitor a severe complication of venetoclax called tumor lysis syndrome (see page 195).

Chemotherapy

Chemotherapy drugs work by attacking cells that grow and multiply very quickly, which is a common characteristic of cancer cells. To learn more about chemotherapy, see Chapter 7 in Part 1 of this guide (page 54)

While the role of chemotherapy is limited in CLL/SLL, it can be used in combination with other drugs like monoclonal antibodies. Examples of chemotherapy agents used in CLL/SLL include the alkylating

agents bendamustine (Bendeke, Treanda), fludarabine (Kudara), and chlorambucil (Leukeran). Most patients with CLL/SLL that are treated with chemotherapy receive treatment as an outpatient (patient receives treatment in the clinic or hospital but is not hospitalized overnight).

Combined Therapies

Some treatment strategies for CLL/SLL use treatment combinations (e.g. chemotherapy or targeted therapy plus monoclonal antibody). For example, monoclonal antibodies like rituximab (Rituxan) or obinutuzumab (Gazyva) are frequently combined with targeted therapy. Other combination therapies used to treat CLL/SLL are listed on Table 17.1. The treating physician will evaluate which combination will provide the best treatment results and lowest risk for each patient.

Stem Cell Transplantation

A stem cell transplant adds new stem cells (blood-forming cells) back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells (see Chapter 7 in Part 1 of this guide). In deciding if transplantation is a good option, doctors consider the patient's health status, age, medical history, cancer stage, and responses to previous therapy.

There are three types of stem cell transplantation that differ based on the source of the stem cells: autologous, allogeneic and syngeneic. Autologous stem cell transplantation is not used in patients with CLL/SLL because their stem cells are often contaminated with the disease. Therefore, this type of stem cell transplantation is not discussed below.

Allogeneic Stem Cell Transplant

In an allogeneic stem cell transplant, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient's child, the patient's parent, an unrelated person, or donated umbilical cord blood (blood from the placenta and umbilical cord that is collected after birth and is rich in stem cells).

Syngeneic Stem Cell Transplant

In a syngeneic stem cell transplant, the donor is the patient's identical twin.

For additional information about the process of stem cell transplantation, please view the *Cellular Therapy* guide on LRF's website at lymphoma.org/publications.

For patients who are not candidates for traditional stem cell transplantation, *reduced-intensity transplantation* (also called nonmyeloablative or mini-allogeneic stem cell transplantation) may be an option. In fact, these are the most commonly used types of transplantations in CLL/SLL patients. This approach uses lower doses of chemotherapy and/or radiation prior to transplantation.

Part 4 — Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chapter 18: Clinical Trials and Advances in Treatment of Patients with CLL/SLL

Overview of Clinical Trials

Drugs that are not yet approved by the FDA are said to be investigational. Some of these investigational drugs are being studied in laboratory experiments. This stage is often referred to as the preclinical phase. The drugs in more advanced stages of research are being studied in patients in clinical trials; these are referred to as being in the clinical phase of development. The most common way for a patient to receive an investigational drug is through a clinical trial.

A *clinical trial* is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is to answer specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment, or the cancer. The investigators in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial.

Clinical trials are not a “last resort” for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments for CLL/SLL must be tested this way before patients can use them in the future. Participating in a clinical trial can help to improve the treatment options for CLL/SLL patients for many years to come. Patients with all stages of CLL/SLL can participate in clinical trials, whether at the time of initial diagnosis or at relapse.

To find out more about getting access to investigational drugs and clinical trials, visit the National Cancer Institute’s (NCI’s) website at www.cancer.gov and search for “access to investigational drugs.” Alternatively, visit www.clinicaltrials.gov to search for trials using a particular drug or to find clinical trials nearby. Patients should check with their doctor

or the Lymphoma Research Foundation (LRF) Helpline “Clinical Trials Information Service” for additional information and recent updates.

See Chapter 8 of this guide for more general information about the topics below:

- What is a Clinical Trial?
- Why Is a Placebo Sometimes Used in Phase III Trials?
- Should a Patient Participate in a Clinical Trial?
- What Is Informed Consent in a Clinical Trial?
- Questions to Ask About a Clinical Trial
- What Is the Cost of Participating in a Clinical Trial?

Advances in Treatment of Patients With CLL/SLL

Doctors and scientists around the world are working very hard to improve currently available treatment options and find better and safer drugs to treat patients with CLL/SLL. Advances are being made in different areas including genetics, molecular biology, immunology, treatments, and supportive care. In particular, recent developments have provided a better understanding of the biology of the disease (how and why the disease develops and spreads). Ongoing research and advances in treatment of patients with CLL/SLL described below.

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cells are a special type of cellular immunotherapy that uses a modified (changed in the laboratory) version of the patient’s T-cells to fight cancer. For more information on CAR T-cell therapy, see Chapter 7 in Part 1 of this guide (page 57). CAR T-cells are currently being studied to treat patients with relapsed or refractory CLL/SLL.

Lisocabtagene maraleucel (Breyanzi) and rapcabtagene autoleucel (YTB-323) are examples of CD19-directed CAR T-cell therapies currently under study for CLL/SLL. Other examples are CLIC-1901, MB-CART19.1 and CTX112. MB-106 is an anti-CD20 CAR T-cell therapy and is also in clinical trials for CLL/SLL.

Some patients have had very good responses to CAR T-cell therapy, with no malignant tumor cells detected after treatment. However, this therapy has different types of potentially serious side effects such as cytokine release syndrome (a condition caused by a large, rapid release of cytokines into the blood from immune cells). Medicines are now available to stop or relieve many of these symptoms. Research is ongoing to continue to improve this novel therapy.

Stem Cell Transplantation

Ongoing research in stem cell transplantation is focused on finding better ways to collect stem cells from the bone marrow or peripheral blood; reducing or eliminating *graft-versus-host disease* in allogeneic transplants; improving ways to remove all lymphoma/leukemia cells from stem cell samples used for autologous transplants; and developing more effective regimens for reduced-intensity stem cell transplantations. For more information on transplantation, please view LRF's Understanding Cellular Therapy booklet available at lymphoma.org/publications.

Immunotherapy

Monoclonal antibodies

Monoclonal antibodies like rituximab (Rituxan, an anti-CD20 antibody), alemtuzumab (Campath, an anti-CD52 antibody), and obinutuzumab (Gazyva, an anti-CD20 antibody) are approved by FDA for the treatment of patients with CLL/SLL. New combinations of these monoclonal antibodies and other novel medications are being investigated in clinical trials. Tafasitamab (Monjuvi, an anti-CD19 monoclonal antibody) is currently being evaluated in clinical trials for patients with CLL. Other monoclonal antibodies in clinical trials include cirmtuzumab (UC-961), targeting receptor tyrosine kinase-like orphan receptor 1 (ROR1). XmAb5574 (MOR00208), a CD19-directed monoclonal antibody, is also being tested for the treatment of patients with CLL/SLL.

Bispecific antibodies

Bispecific antibodies bind to two different antigens which can be located at the surface of the same or 2 different cells. Examples of bispecific antibodies under study for relapsed/refractory CLL include epcoritamab (Epkinyt) and mosunetuzumab (Lunsumio), which bind to the patient's

healthy T-cells (a type of white blood cell) that express CD3 and cancer cells that express CD20. Ixcentamab (GEN3009), a bispecific antibody directed at two different parts of CD37 (a marker in cancerous B-cells), is also being studied in patients with relapsed or refractory CLL/SLL.

Immune Checkpoint inhibitors

Immune checkpoint inhibitors help develop or enhance the immune system's capacity to kill cancer cells that evade the immune system's response. Two checkpoint inhibitors, nivolumab (Opdivo) and pembrolizumab (Keytruda), which are FDA-approved for the treatment of Hodgkin lymphoma, are currently being investigated in CLL/SLL clinical trials. Atezolizumab (Tecentriq) is also under investigation for the treatment of CLL/SLL.

Vaccines

Vaccines are commonly used to help protect against viruses and other infections. In these cases, researchers are focused on developing vaccines to help treat, rather than prevent, lymphomas. The hope is that these vaccines might boost the immune system to recognize and kill cancer cells early during the course of the disease.

Targeted therapies

Several targeted therapies for CLL/SLL are being studied in laboratories and in clinical trials, like the BTK inhibitor nemtabrutinib (MK-1026). MS-553, an inhibitor of protein kinase C (PKC), is also in clinical trials for the treatment of CLL/SLL. Since research in CLL/SLL advances quickly, patients should check with their doctor or LRF for additional information and updates.

Chemotherapy

Researchers are trying to develop new chemotherapy drugs, improve existing drugs, and find better ways to combine different dosages and sequences of existing drugs. The goal is to develop treatment regimens that are better at killing CLL/SLL cells while leaving healthy cells alone, decreasing the chance of side effects.

Combination Therapies

Many treatment strategies testing new treatment combinations are currently in clinical trials for patients with newly diagnosed or previously treated CLL/SLL.

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**Lymphoma Research Foundation
(LRF) Helpline and Clinical Trials
Information Service**

CONTACT THE LRF HELPLINE

Trained staff are available to answer questions and provide support to patients, caregivers and healthcare professionals in any language.

Our support services include:

- Information on lymphoma, treatment options, side effect management and current research findings
- Financial assistance for eligible patients and referrals for additional financial, legal and insurance help
- Clinical trial searches based on patient's diagnosis and treatment history
- Support through LRF's Lymphoma Support Network, a national one-to one volunteer patient peer program

Monday through Friday
9:30 am – 7:30 pm Eastern Standard Time (EST)
Toll-Free (800) 500-9976
or email helpline@lymphoma.org

