

Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma: Relapsed/Refractory

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are forms of *low-grade* (slow growing) non-Hodgkin lymphoma that develop from white blood cells called lymphocytes.

CLL and SLL are basically the same disease, with the only difference being the location of the primary cancer. In CLL, cancer cells are located in the bloodstream and the bone marrow (the spongy tissue inside the bone). In SLL, the cancer cells are located mainly in the lymph nodes (small bean-shaped structures that help the body fight disease; Figure 1). Patients with lymphoma that involves both the blood and lymph nodes often use the terms CLL and SLL interchangeably.

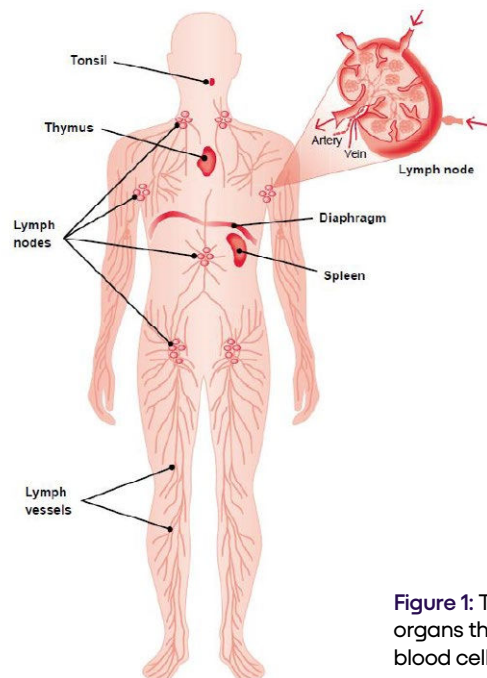


Figure 1: The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.

The natural history of CLL/SLL (how the disease evolves) has changed dramatically in recent years with the development of *oral targeted therapies* (drugs taken by mouth that target specific molecules cancer cells use to grow and/or spread). Many patients with CLL/SLL do not require treatment at diagnosis and are monitored through *active surveillance* from months to years thereafter. In this case, the patient's condition is monitored closely but not treated, unless symptoms appear, or the disease worsens. Other patients with CLL/SLL respond to initial treatment and go into *remission* (disappearance of signs and symptoms). In some cases, the cancer becomes *refractory* (stops responding to treatment) or relapses (disease returns after treatment). For patients whose disease relapses or is refractory, different therapies may result in improved outcomes and remission. However, most patients with CLL/SLL respond to treatment and refractory disease is rare.

For more information about CLL/SLL diagnosis, please view the *Understanding Lymphoma and CLL Guide* on the Foundations website (visit lymphoma.org/publications).

Treatment Options

Chemotherapy (drugs that stop the growth of or kill cancer cells) plays a **limited** role in the management of CLL. Most patients are now treated with:

- Targeted therapy (drugs that target specific molecules that cancer cells use to survive and spread). This includes inhibitors of proteins involved in cell signaling and growth like kinases.
- Immunotherapy (drugs that help the body's immune system fight cancer).
 - Monoclonal antibodies (a protein made in the laboratory that binds to cancer cells and help the immune system destroy them) such as rituximab (Rituxan). Patients seeking information about targeted therapy and immunotherapy should view the *Immunotherapy and Other Targeted Therapies in Lymphoma* fact sheet on the Foundation's website (lymphoma.org/publications)
- Stem cell transplantation (SCT, the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells).
 - *Allogeneic* SCT (blood-forming cells donated from a living donor) can potentially cure the disease, but it is rarely used due to the high risk of complications. For more information on Allogeneic SCT, view the *Understanding Cellular Therapy* guide on the Foundation's website (lymphoma.org/publications).

Treatment for relapsed/refractory disease is based on the following factors:

- Patient's age and overall health.
- Where the cancer is located.
- How severe the disease is.
- Previous treatment (how long and how well the patient responded to other therapies).

Treatment may depend on the identification of specific markers (proteins found at the surface cancer cells) and whether these cells have certain *mutations* (permanent changes) in the DNA (deoxyribonucleic acid, the molecule that carries genetic information inside the cell). This will help doctors learn more about cancer and evaluate what is the best treatment for you.

Approved targeted therapy drugs or drug combinations for relapsed/refractory CLL/SLL include:

- Ibrutinib (Imbruvica).
- Acalabrutinib (Calquence).
- Venetoclax (Venclexta) +/- rituximab (Rituxan).
- Zanubrutinib (Brukinsa).
- Duvelisib (Copiktra).
- Pirtobrutinib (Jaypirca).
- Lisocabtagene ciloleucel (Breyanzi).

Various other treatments are available or in development and should be discussed with your physician and/or with a physician that specializes in CLL.

Patients seeking information for newly diagnosed disease should view the *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma* fact sheet on Lymphoma Research Foundation's website (lymphoma.org/publications).

Treatments Under Investigation

Many new treatments (also referred to as investigational drugs) and combinations are currently being tested in clinical trials for patients with relapsed/refractory CLL/SLL. Results from these trials may improve or change the current standard of care (the proper treatment that is widely used by health care professionals and accepted by medical experts). **Table 1** (below) lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the *Understanding Clinical Trials* publication on the Lymphoma Research Foundation's website at lymphoma.org/publication.

Table 1: Investigational drugs for relapsed or refractory CLL/SLL

Agent (drug)	Class (type of treatment)
Lisaftoclax (APG-2575)	Targeted therapy; Bcl-2 inhibitor
Sonotoclax (BGB-11417)	Targeted therapy; Bcl-2 inhibitor
Daratumumab (Darzelex)	Immunotherapy; anti-CD38 antibody
Lisocabtagene maraleucel (Breyanzi)	CAR T cell therapy; anti-CD19
KRT-232	Targeted therapy; MDM2 inhibitor
Nemtabrutinib (MK-1026)	Targeted therapy; BTK inhibitor
Nivolumab	Immunotherapy; PD-1 checkpoint inhibitor
MS-553	Targeted therapy; PKC-β inhibitor
MOR00208	Immunotherapy; anti-CD19 antibody
Orelabrutinib (ICP-022)	Targeted therapy; BTK inhibitor
Pembrolizumab (Keytruda)	Immunotherapy; PD-1 checkpoint inhibitor
TL-895	Targeted therapy; tyrosine kinase inhibitor
TQB-3909	Targeted therapy; Bcl-2 inhibitor
Atezolizumab	Immunotherapy; PD-1 checkpoint inhibitor

Bcl-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; MDM2, murine double minute 2; PD-1, programmed cell death protein 1; PKC-β, protein kinase C beta.

Clinical Trials

Clinical trials are crucial for identifying effective drugs and optimal treatment doses for patients with lymphoma. Every patient being treated for CLL should request their care team to discuss clinical trial options before making a final decision on treatment choice. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (lymphoma.org/publications), talk to their physician, or contact the Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing helpline@lymphoma.org.

Minimal Residual Disease

Minimal residual disease (MRD, or measurable residual disease) refers to the small number of cancer cells in the body after completion of treatment. Typically, MRD tests detect cancer cells that remain in the blood or bone marrow and is often done in clinical trials. Using very sensitive laboratory methods, one cancer cell can be detected among 1,000,000 healthy blood cells. An MRD-negative test means that there are no cancer cells detected with the laboratory methods that were used. Testing for MRD is mostly used as a prognostic marker (predicts how well the patient will do) that provides useful information about long-term outcome after treatment. The prognostic value (the ability to predict how well the patient will do) of MRD may be dependent on the treatment the patient is receiving.

For some CLL therapies, studies have found that patients with lower levels of MRD (fewer cancer cells remaining after the completion of treatment) have a longer remission. Patients receiving Bruton's tyrosine kinase (BTK) inhibitors (a type of drug that works by blocking a specific protein called BTK, which the cancer cells use to survive and spread) typically do not reach a negative MRD status. However, the response to treatment can still last for a long period and maintain disease control for many years. For this reason, having detectable MRD does not necessarily mean the disease has relapsed or become refractory. This will help to make individualized decisions for your case. More recent studies are investigating whether undetectable MRD may result in shorter courses of treatment for patients. Patients should be encouraged to discuss MRD with their physician or a physician specialized in CLL/SLL. If your doctor decides to test for MRD, it is important to discuss what your MRD status is and what does it mean. Patients seeking information about MRD should view the *Minimal Residual Disease in Lymphoma* fact sheet on the Foundation's website (lymphoma.org/publications)

Follow-up

Because multiple disease relapses are frequent in CLL/SLL, patients in remission should have regular visits with their physician. During these visits, medical tests (such as blood tests and computed tomography [CT] scans) may be required to evaluate the need for additional treatment.

Some treatments can cause long-term side effects (occur **during** treatment and continue for months or years) or late side effects (appear only months, years, or decades **after** treatment has ended). These side effects can vary depending on the following factors:

- Duration of treatment (how long the treatment lasted).
- Frequency of treatment (how often was the treatment administered).
- Type of treatment given.
- Age and gender of the patient.
- Patient overall health at the time of their treatment.

A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the patient stays in remission.

Patients and their care partners are encouraged to keep copies of all medical records. This includes test results as well as information on the type, amount, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation's award-winning *Focus On Lymphoma* mobile app can help patients manage this documentation.

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. The Foundation's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting lymphoma.org/publications.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit lymphoma.org/programs.

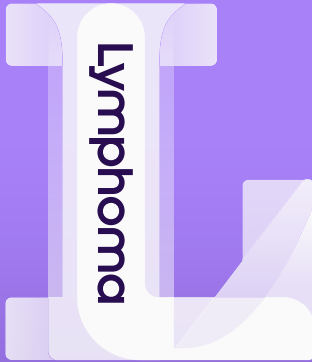
Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at lymphoma.org, or contact the Helpline at (800) 500-9976 or helpline@lymphoma.org.

Para información en Español, por favor visite lymphoma.org/es. (For information in Spanish please visit lymphoma.org/es).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at lymphoma.org/mobileapp, or contact the Foundation's Helpline at (800) 500-9976 or helpline@lymphoma.org.



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