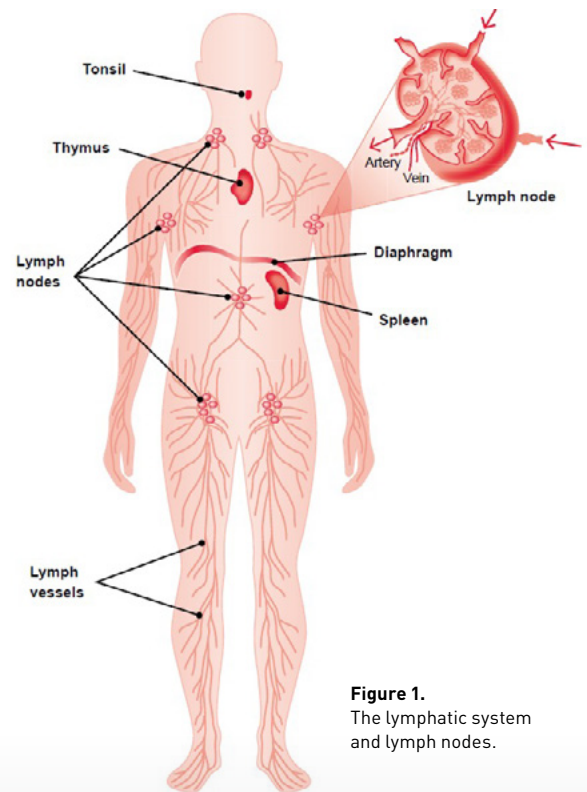


# Understanding Lymphoma: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Relapsed/Refractory

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  
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 (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.

## TREATMENT OPTIONS

Chemotherapy 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) or immunotherapy (drugs that help the body's immune system fight cancer). Patients seeking information about targeted therapy and immunotherapy should view the *Biologic and Novel Therapies in Lymphoma* fact sheet on Lymphoma Research Foundation's (LRF's) website ([lymphoma.org/publications](http://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 genetic mutations (permanent changes) in the DNA (deoxyribonucleic acid; the molecule that carries genetic information inside the cell). This will help doctors learn more about the cancer and evaluate what is the best treatment for you.

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

- Ibrutinib (Imbruvica)
- Acalabrutinib (Calquence)
- Venetoclax (Venclexta) +/- rituximab (Rituxan)
- Zanubrutinib (Brukinsa)
- Duvelisib (Copiktra)

Various other treatments are available or in development and should be discussed with your physician and/or with a physician that specializes in CLL. An allogeneic stem cell transplant (ASCT; cells donated from a living donor) can potentially cure the disease, but it is rarely used due to a higher risk of complications. For more information on ASCT, view the *Understanding Cellular Therapy* guide on the LRF's website ([lymphoma.org/publications](http://lymphoma.org/publications)).

Patients seeking information for newly diagnosed disease should view the *Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma* fact sheet on LRF's website ([lymphoma.org/publications](http://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* fact sheet on the LRF's website at [lymphoma.org/publication](http://lymphoma.org/publication).

Table 1. Investigational Drugs for Newly Diagnosed CLL/SLL

Agent (Drug)	Class (Type of Treatment)
Lisaftoclax (APG-2575)	Targeted therapy; BCL-2 inhibitor
BN102 (AS-1763)	Targeted therapy; BTK inhibitor
BGB-11417	Targeted therapy; BCL-2 inhibitor
Daratumumab (Darzelex)	Immunotherapy; anti-CD38 antibody
DTRMWXHS-12	Targeted therapy; BTK inhibitor
Lisocabtagene maraleucel (Breyanzi)	CAR T-cell therapy; anti-CD19
KRT-232	Targeted therapy; MDM2 inhibitor
MOR00208	Immunotherapy; anti-CD19 antibody
Nemtabrutinib (MK-1026)	Targeted therapy; BTK inhibitor
MS-553	Targeted therapy; PKC-β inhibitor
NVG-111	Immunotherapy; anti-CD3 & -ROR1 bispecific antibody
Orelabrutinib (ICP-022)	Targeted therapy; BTK inhibitor
Pembrolizumab (Keytruda)	Immunotherapy; PD-1 checkpoint inhibitor
Pirtobrutinib (LOXO-305)	Targeted therapy; BTK inhibitor
TL-895	Targeted therapy; tyrosine kinase inhibitor
TQ-B3525	Targeted therapy; PI3K inhibitor
Ublituximab (TG-1101)	Immunotherapy; anti-CD20 antibody
Umbralisib (Ukoniq)	Targeted therapy; PI3K-delta and CK1-epsilon inhibitor
Zandelisib (ME-401)	Targeted therapy; PI3K inhibitor
Atezolizumab	Immunotherapy; PD-1 checkpoint inhibitor

BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CCR-7, C-C chemokine receptor type 7; CDK, cyclin-dependent kinase; CK, casein kinase; MDM2, murine double minute 2; PD-1, programmed cell death protein 1; PI3K, phosphatidylinositol 3-kinase; PKC-β, protein kinase C beta; ROR1, receptor tyrosine kinase orphan like receptor 1.

## 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 LRF's website ([lymphoma.org/publications](http://lymphoma.org/publications)), talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing [helpline@lymphoma.org](mailto: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 making 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 it means.

## 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 the treatment was administered)
- Type of treatment given
- Patient's age and gender
- Patient's 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 caregivers 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. LRF's award-winning *Focus on Lymphoma* mobile app can help patients manage this documentation.

## LYMPHOMA CARE PLAN AND PATIENT EDUCATION PROGRAMS

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. LRF's *Lymphoma Care Plan* fact sheet 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* fact sheet can be accessed by visiting [lymphoma.org/publications](http://lymphoma.org/publications). LRF also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit [lymphoma.org/programs](http://lymphoma.org/programs).

## LRF Helpline

The LRF Helpline staff is 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. LRF 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](http://lymphoma.org), or contact the LRF Helpline at **(800) 500-9976** or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

Para información en Español, por favor visite [lymphoma.org/es](http://lymphoma.org/es). (For Information in Spanish, please visit [lymphoma.org/es](http://lymphoma.org/es)).



## LRF FOCUS ON LYMPHOMA MOBILE APP

*Focus on Lymphoma* is the first app to provide patients and their caregivers with tailored content based on lymphoma subtype and actionable tools to better manage diagnosis and treatment. Experience 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 LRF content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more this resource, visit our website at [lymphoma.org/mobileapp](http://lymphoma.org/mobileapp), or contact the LRF Helpline at **800-500-9976** or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

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Supported through grants from:

The *Understanding Lymphoma* fact sheet series is published by the Lymphoma Research Foundation (LRF) for the purpose of informing and educating readers. Facts and statistics were obtained using published information, including data from the Surveillance, Epidemiology, and End Results (SEER) Program. Because each person's body and response to treatment is different, no individual should self-diagnose or embark upon any course of medical treatment without first consulting with his or her physician. The medical reviewer, the medical reviewer's institution, and LRF are not responsible for the medical care or treatment of any individual.