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).

Many patients with CLL/SLL will live for years without any obvious symptoms. The disease might be detected during routine blood tests and/or a physical examination. Other patients may have symptoms that cause them to seek care from a doctor, and testing may lead to the diagnosis of CLL/SLL. Symptoms depend on the tumor location and may be mild. The most common symptoms are:

- Fatigue (extreme tiredness)
- Shortness of breath
- Bleeding or bruising easily
- Bone pain
- Night sweats
- Weight loss
- Frequent infections

Less frequent symptoms are often related to enlarged lymph nodes or spleen and may cause discomfort or a feeling of fullness after eating small amounts.

**TREATMENT OPTIONS**

Treatment is based on the severity of symptoms. When patients show no or few symptoms, doctors may decide to monitor the patient without treating the disease. This approach is called “active surveillance”, or “watchful waiting”. In this case, patients’ overall health and disease are monitored through regular check-up visits that may include laboratory tests (like a complete blood cell count) and physical examinations (like checking for any swelling). Sometimes, patients experience symptoms due to low red blood cell count (anemia). If patients begin to have symptoms or signs of disease progression, treatment is then prescribed.
There are many current frontline (initial) treatment options for CLL/SLL. Treatments might differ in the presence of certain genetic mutations (permanent changes in the DNA [deoxyribonucleic acid, the molecule that carries genetic information inside the cell]). An oncologist (a doctor who specializes in treating cancer) or hematologist (a doctor who specializes in treating blood cancers and other blood disorders) will run a variety of tests in order to confirm a person’s diagnosis and decide the appropriate treatment, if needed. The patient’s age, health status, and the benefits versus side effects of treatment are also considered for treatment decision. To learn more about how doctors establish a treatment plan for CLL/SLL, please view the Understanding Lymphoma guide on Lymphoma Research Foundation’s website (lymphoma.org/publications).

Newer drugs and combinations have shown excellent activity in patients with all sorts of disease characteristics. Initial treatments for CLL/SLL include targeted therapy (drugs that target specific molecules that cancer cells use to survive and spread) and immunotherapy (drugs that help the body’s immune system fight cancer). Patients seeking information about targeted therapy and immunotherapy should view the Immunotherapy and Other Targeted Therapies fact sheet on LRF’s website (lymphoma.org/publications). Common drugs or drug combinations for newly diagnosed CLL/SLL include:

- Venetoclax (Venclexta) +/- obinutuzumab (Gazyva)
- Acalabrutinib (Calquence) +/- obinutuzumab (Gazyva)
- Zanubrutinib (Brukinsa)
- Ibrutinib (Imbruvica) +/- rituximab (Rituxan)
- Ibrutinib (Imbruvica) and obinutuzumab (Gazyva)

Occasionally, patients might also be treated with chemotherapy. Chemotherapy plays a limited role in the treatment of CLL nowadays. Treatment decisions depend on specific patient factors, like the ones mentioned above, and should be discussed extensively with the patient’s physician, ideally one that specializes in CLL. There are other combinations of treatments that may be suggested. These include chemotherapy and immunotherapy regimens like the ones listed below:

- FCR (fludarabine [Fludara], cyclophosphamide [Cytoxan], rituximab [Rituxan])
- GC (obinutuzumab [Gazyva] and chlorambucil [Leukeran])
- BR (bendamustine [Beltrapzo/Bendeka/Treanda] and rituximab [Rituxan])
- Rituximab (Rituxan) or obinutuzumab (Gazyva) with corticosteroids such as dexamethasone and prednisone
- Obinutuzumab (Gazyva)

For patients who relapse (disease returns after treatment) or whose disease becomes refractory (does not respond to treatment), different therapies may result in improved treatment outcomes. Patients seeking information about relapsed/refractory disease should view the Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Relapsed/Refractory fact sheet on LRF’s website (lymphoma.org/publications).

The following are common therapeutic regimens for relapsed/refractory CLL and SLL:

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

Various other treatments are available or in development and should be discussed with your physician and/or a physician specialized in CLL. An allogeneic stem cell transplant (ASCT, cells donated from a living donor) is a potentially curative option. However, most patients will do well with newer treatments that avoid the risk of the complications of transplants. For more information on ASCT, view the Understanding Cellular Therapy publication on the LRF’s website at 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 newly diagnosed or previously treated CLL/SLL. Results from these clinical 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 (LRF’s) website at lymphoma.org/publications (Table 1).

Researchers are also investigating ways to improve ASCT in patients with CLL/SLL. In addition, a special type of immunotherapy called chimeric antigen receptor (CAR) T-cell therapy uses patients’ own immune cells to treat their cancer. Several CAR T-cell therapies are in development for patients with CLL/SLL. For more information on CAR T-cell therapy, view the Understanding Cellular Therapy guide on the Lymphoma Research Foundation’s (LRF’s) website at lymphoma.org/publications.
Trials Search Request Form

by calling or contact the LRF Helpline for an individualized clinical trial search

Trials participating in a clinical trial should view the treatment doses for patients with lymphoma. Patients interested in discussing what your MRD status is and what it means. CLL/SLL. If your doctor decides to test for MRD, it is important to discuss MRD with their physician or a physician specialized in course of treatment for patients. Patients should be encouraged investigating whether undetectable MRD may result in a shorter individualized decisions for your case. More recent studies are has relapsed or become refractory. This will help making having detectable MRD does not necessarily mean the disease maintain disease control for many years. For this reason, inhibitors may not reach a negative MRD status. However, receiving treatment with Bruton’s tyrosine kinase (BTK)

the completion of treatment) have a longer remission. Patients with lower levels of MRD (fewer cancer cells remaining after completion of treatment) have a longer remission. Patients receiving treatment with Bruton’s tyrosine kinase (BTK) inhibitors may 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 a shorter course 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.

**CLINICAL TRIALS**

Clinical trials are crucial in identifying effective drugs and optimal treatment doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the Understanding Clinical Trials fact sheet ([lymphoma.org/publications](http://lymphoma.org/publications)) and the Clinical Trials Search Request Form ([lymphoma.org](http://lymphoma.org)), 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.

**MINIMAL RESIDUAL DISEASE**

Minimal residual disease (MRD) 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. Testing for MRD 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 within the sensitivity of the method used. Testing for MRD is mostly used as a prognostic marker (predicts the likely course of the disease) that provides useful information about long-term outcome after treatment. The prognostic value of MRD may be dependent on the treatment the patient is receiving.

With certain 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 treatment with Bruton’s tyrosine kinase (BTK) inhibitors may 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 a shorter course 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 disease relapses do occur 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 recommended 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
- Age and gender of the patient
- Patient overall health at the time of their treatment

A physician and their care team 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 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. 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.

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**Table 1. Investigational drugs for newly diagnosed CLL/SLL.**

<table>
<thead>
<tr>
<th>Agent (Drug)</th>
<th>Class (Type of treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirmtuzumab (UC-961)</td>
<td>Immunotherapy; anti-ROR1 antibody</td>
</tr>
<tr>
<td>Orelabrutinib (ICP-022)</td>
<td>Targeted therapy; BTK inhibitor</td>
</tr>
<tr>
<td>Pirtobrutinib (LOXO-305)</td>
<td>Targeted therapy; BTK inhibitor</td>
</tr>
<tr>
<td>Nemabrutinib (MK-1026, ARQ 531)</td>
<td>Targeted therapy; BTK inhibitor</td>
</tr>
</tbody>
</table>

BTK, Bruton’s tyrosine kinase; ROR1, receptor tyrosine kinase-like orphan receptor 1.
The LRF 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. 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, or contact the LRF 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).

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