

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

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are forms of low grade (grows very slowly) non-Hodgkin lymphoma (NHL) that arise from white blood cells called lymphocytes.

CLL and SLL are essentially the same disease, with the only difference being the location where the cancer primarily occurs. When most of the cancer cells are located in the bloodstream and the bone marrow, the disease is referred to as CLL. When the cancer cells are located mostly in the lymph nodes and are less frequent in the blood, the disease is called SLL.

The outlook for patients with CLL/SLL has improved in recent years, but the disease course still varies widely. Many patients will be diagnosed by their primary care physician based on abnormal blood work despite having no symptoms. These patients often do not require treatment at diagnosis and perhaps for months to years thereafter. Other patients with CLL/SLL develop symptoms related to their disease and will receive treatment. They will hopefully respond to initial treatment and go into *remission* (disappearance of signs and symptoms). Others experience a *refractory* (does not respond to treatment) disease course, and their cancer stops responding to *frontline* (initial) therapy or *relapses* (disease returns after treatment). For patients whose disease becomes refractory or relapses, subsequent therapies may be successful in providing another remission.



TREATMENT OPTIONS

Traditional intravenous Chemotherapy plays a very limited role in the management of CLL. Most patients are now treated with targeted therapy or immunotherapy. Treatment at all stages of the disease is based on the patient's age and overall health, and the extent and location of disease. Additionally, the type of previous therapies received and the length of response to previous therapies should be considered. Treatment may depend on the identification of markers found on cancer cells and whether the patient's lymphoma cells have certain genetic alterations. Preferred regimens for the treatment of relapsed/refractory disease include:

- Ibrutinib (Imbruvica) +/- rituximab (Rituxan) or obinutuzumab (Gazyva)
- Venetoclax (Venclexta) +/- rituximab (Rituxan) or obinutuzumab (Gazyva)
- Idelalisib (Zydelig) and rituximab (Rituxan) or obinutuzumab (Gazyva)
- Acalabrutinib (Calquence) +/- rituximab (Rituxan) or obinutuzumab (Gazyva)
- Duvelisib (Copiktra)
- Immunotherapy (lenalidomide) +/- rituximab.

Patients seeking information for newly diagnosed disease should view the *Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma* fact sheet on Lymphoma Research Foundation's (LRF's) website (click [here](#)).

Biosimilar therapies (drugs that are modeled after an existing biologic therapy) may be an option for patients who are taking rituximab. These include rituximab-abbs and rituximab-pvvr. For more information on biosimilar therapies visit lymphoma.org/publications for our *Biosimilar Therapies* factsheet. Multiple other agents are available and treatment selection is often dictated by specific patient factors. Options should be discussed with the patient's oncologist or hematologist, and ideally one that specializes in CLL.

An *allogeneic stem cell transplant* (cells donated from a living donor) is a potentially curative option, but it is rarely used due to substantial risk of complications.

TREATMENTS UNDER INVESTIGATION

Many treatments are currently being tested in clinical trials for patients with relapsed/refractory CLL/SLL (Table 1). Another area of research for treating CLL is genetically engineered T cells designed to recognize and kill cancer cells, referred to as chimeric antigen receptor (CAR) T-cell therapy. Finally, researchers are also investigating ways to improve stem cell transplantation in patients with CLL/SLL. It is critical to remember that today's scientific research is continuously evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged.

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

AGENT	CLASS
Pirtobrutinib (LOXO 305)	Targeted therapy; BTK inhibitor
DTRMWXHS-12	Targeted therapy; BTK inhibitor
Ublituximab (TG-1101)	Immunotherapy; anti-CD20 antibody
Umbralisib (Ukoniq)	Targeted therapy; PI3K-delta and CK1-epsilon inhibitor
Nivolumab (Opdivo)	Immunotherapy; PD-1 checkpoint inhibitor
Tafasitamab (Monjuvi)	Immunotherapy; anti-CD19 antibody
APG-2575	Targeted therapy; Bcl-2 inhibitor
AT-101	Targeted therapy; Bcl-2 inhibitor
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor
Lisocabtagene maraleucel	CAR T cell therapy; anti-CD19
PBCAR20A	CAR T cell therapy; anti-CD20

Bcl-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; CK, casein kinase; PD-1, programmed cell death protein 1; PI3K, phosphatidylinositol 3-kinase.

CLINICAL TRIALS

Clinical trials are crucial for identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the Understanding Clinical Trials fact sheet on LRF's website (click [here](#)), 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

Testing for *minimal residual disease* (MRD, or measurable residual disease) is often done in clinical trials to detect cancer cells that remain in the blood or bone marrow after the completion of treatment. Using very sensitive laboratory techniques, one abnormal cell can be detected among 1,000,000 healthy blood cells. Studies have found that patients with lower levels of MRD (fewer cancer cells remaining after the completion of treatment) may have a longer remission. Studies are underway to investigate whether MRD testing may be used to shorten the course of treatment for patients with undetectable levels of cancer cells in their blood before they have completed a full course of therapy. Testing for MRD may be appropriate in some instances and patients should discuss with their doctor if this test would be helpful in their care.

FOLLOW-UP

Because multiple disease relapses are frequent in CLL/SLL, patients in remission should have regular visits with a physician who is familiar with their medical history and the treatments they have received. Medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term side effects or late side effects, which can vary based on the duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any side effects resulting from treatment or potential disease recurrences. LRF's award-winning *Focus On Lymphoma* mobile app (lymphoma.org/mobileapp) can help patients manage this documentation.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and CLL/SLL, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to webinars for people with lymphoma, as well as an *Understanding Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma* patient guide and CLL/SLL e-Updates that provide the latest disease-specific news and treatment options. To learn more about any of these resources, visit our websites at lymphoma.org/CLL or lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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Supported through grants from:



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Last updated 2021

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