

Understanding Your Relapsed or Refractory CLL/SLL Diagnosis and Treatment Options

The goal of this resource is to increase your understanding of chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL), particularly when the disease returns or stops responding to treatment. This is known as relapsed or refractory disease. Knowledge and understanding make you better equipped to partner in decision-making with your oncology care team so you can receive the best personalized care.

What is CLL/SLL?

CLL has the word “chronic” in its name, meaning most people live with the cancer for many years. This is called having a slow-growing cancer. CLL is a cancer of a type of white blood cell called lymphocytes. There are different types of lymphocytes, and in CLL, it is a B-cell or a B-lymphocyte that becomes cancerous. Normal B-lymphocytes help to fight infection. CLL occurs when one abnormal B-lymphocyte is damaged and grows out of control, creating many duplicates of itself. In CLL, these duplicating cancer cells are found mostly in the blood and bone marrow. In SLL, cancer cells are found mostly in the lymph nodes. CLL and SLL are the same disease. When you were diagnosed, you may have been told that you have SLL because of where the cancer was primarily located at the time. Later, you may have been told that you have CLL because now more of the cancer is in the circulating blood. This does not mean you have 2 different types of cancer. It is the same cancer and treated with the same therapies.

What is relapsed or refractory CLL, and how is it treated?

Relapsed CLL is when the disease reappears or becomes worse after at least 6 months since the last time you responded to treatment. On the other hand, refractory CLL means your disease has not responded or has become worse within 6 months of **starting** treatment. Although this may sound discouraging, the good news is that there are many different treatment options you can explore.

Treatment for CLL, including relapsed and refractory disease, has evolved substantially during the past decade. Whereas in the past most patients received chemoimmunotherapy, the majority of patients now receive targeted therapies, which are generally safer and more effective.

In fact, most patients with CLL will need different types of treatment over time. In relapsed or refractory CLL, additional testing can help guide the choice of next therapy. Patients may transition to other treatments such as BTK inhibitors, BCL-2 inhibitors, or antibody-based therapies depending on prior treatment and disease response. Clinical trials may also provide access to emerging treatment options.

Below is a table of some of the most common therapies to date for relapsed or refractory CLL/SLL.

	Mechanism	EMA Approval	Administration
Zanubrutinib	BTK inhibitor, covalent	Previously treated or untreated	Pills taken 1-2 times daily ¹⁻⁷
Acalabrutinib	BTK inhibitor, covalent	Previously treated or untreated; can be used in combination with venetoclax and/or obinutuzumab (only in untreated)	
Ibrutinib	BTK inhibitor, covalent	Previously treated or untreated patients with or without 17p deletion; it may be used in combination with venetoclax in previously untreated patients	

Mechanism		EMA Approval	Administration
Pirtobrutinib	BTK inhibitor, noncovalent	Previously treated with a covalent BTK inhibitor	Pills taken 1-2 times daily ¹⁻⁷
Venetoclax	BCL-2 inhibitor	Previously untreated (in combination with obinutuzumab) or previously treated as monotherapy or in combination with rituximab	
Idelalisib	PI3K inhibitor	Previously treated after at least 2 previous therapies or, for idelalisib, in combination with rituximab	
Duvelisib			
Obinutuzumab	CD20 antibody (an antibody treatment that targets a specific molecule on the B-cell)	Previously untreated CLL	IV infusion or injection under the skin ⁸
Rituximab	CD20 antibody	As monotherapy or in combination with venetoclax in pretreated patients	IV infusion or injection under the skin ⁹

There are additional treatments available, including chemoimmunotherapy (such as fludarabine, cyclophosphamide, rituximab) or hematopoietic stem cell transplant. Clinical trials can also be a strong option.

The following table includes some of the key factors to think about with different treatment options for CLL.

Factor	Impact on Treatment Decisions
Administration of treatment (oral, intravenously)	- Venetoclax is taken orally but is usually combined with anti-CD20 antibodies, which are administered intravenously - BTK inhibitors are oral medications - CAR T-cell therapy and many associated treatments are administered intravenously
Length of treatment (for a limited duration of time or continuously until the medication no longer controls the disease)	- Venetoclax is recommended to be taken for 1 year in the first-line setting and 2 years in second-line or later settings - BTK inhibitors are usually taken continuously until disease progresses or the drug must be stopped because of toxicity - A fixed-duration treatment regimen may be an option with some BTK inhibitors in combination with venetoclax
Common side effects of the different treatments	Different treatment regimens have different side effect profiles; these should be discussed with your treatment team before deciding on a treatment course
Other illnesses (comorbidities) and medications	Your other conditions and medications can influence the safest and most effective therapy
Future therapies	Most patients will need more than 1 therapy, so it is important to understand how one therapy might affect subsequent options
Financial considerations	Will the medication be covered by your insurance? What is your out-of-pocket expense? If not or only partially covered, are there any ways to obtain the treatment through other means, such as medication assistance programs?

Working together: how to figure out which treatment is right for you

It is important to make sure you receive the correct therapy and know that you have multiple treatment options and backups if a specific treatment is not working for you. Treatment options have advanced in the past decade, and it is now common to receive targeted therapy instead of chemoimmunotherapy. CLL can be observed and monitored, so treatment might not be necessary, especially if you have early disease and/or no symptoms. Think carefully about your personal expectations, desires, and hopes for treatment and how treatment will affect your life. Be sure to express certain preferences to your doctor so the best treatment option can be selected for you.

Below is a list of questions to ask your hematologist/oncologist when picking a treatment regimen.

Understanding your specific diagnosis:

- ☐ Am I a good candidate for treatment, and if so, what kind of treatment is right for me?

- ☐ Is there anything about my CLL that would make the cancer more difficult to treat? Specifically, what is my disease stage and molecular features (IGHV and TP53/del[17p])?

Treatment-related questions:

- ☐ How often and for how long will I need to be treated?

- ☐ Should I take a combination of therapies or just one?

- ☐ How will I be monitored while taking the therapy?

- ☐ What are the possible short-term and long-term side effects of treatment?

- ☐ Which side effects do I need to report right away? If that happens, do I call you, the cancer clinic, or my family doctor, or go to the emergency room?

- ☐ How will I feel during the treatment?

Additional questions:

- ☐ Should I be worried about my risk for infection? What should I do to protect myself?

- ☐ Which doctor(s) will manage my care?

- ☐ How much does treatment cost? Is the cost of the therapy covered by insurance/publicly funded?

☐ Am I eligible for any clinical trials?

☐ Is there an oncology social worker available for support and financial information?

If you have additional questions, make sure you write them down before the appointment and prioritize the most important.

Make sure you have a way to record the answers such as a notebook, tablet, or your phone. Consider asking the healthcare professional if you can record the conversation to reference it later.

Bring a family member or friend to the appointment so there is another person there for the conversation. They can help ask questions, record the answers, and provide support during the discussion.

Sources of information

Do you want to understand your disease and treatment options better? You can always ask your hematologist/ oncologist or clinical care nurse, but patient organizations also exist. Check out some of the resources listed in the next table to stay up to date on the latest CLL news, find out about clinical trials or even to connect with other CLL patients for support. Do you want to check out a full list of international organizations? Check out the [Lymphoma Coalition](#).

Organization	Country	Language
ASPA-LLC (Asociación de Pacientes con Leucemia Linfática Crónica)	Spain	Spanish
AIL (Associazione Italiana Contro Leucemie Linfomi e Mieloma)	Italy	Italian
Deutsche Leukämie- und Lymphom-Hilfe eV	Germany	German
ELLYE (Ensemble Leucémie Lymphomes Espoir)	France	French
Blood Cancer United	USA	English and Spanish
CLL Society	USA	English, Chinese, French, German, Italian and Spanish
Lymphoma Research Foundation	USA	English and Spanish

References

1. Zanubrutinib [product information]. Schiphol, The Netherlands: BeOne Medicines I GmbH; 2025.
2. Acalabrutinib [product information]. Södertälje, Sweden: AstraZeneca AB; 2025.
3. Ibrutinib [product information]. Latina, Italy: Janssen-Cilag SpA; 2026.
4. Pirtobrutinib [product information]. Madrid, Spain: Lilly S.A.; 2026.
5. Venetoclax [product information]. Campoverde di Aprilia (Latina), Italy: AbbVie S.r.l.; 2025.
6. Idelalisib [product information]. County Cork, Ireland: Gilead Sciences Ireland UC; 2024.
7. Duvelisib [product information]. Stamullen, Ireland: Millmount Healthcare Limited; 2025.
8. Obinutuzumab [product information]. Grenzach-Wyhlen, Germany: Roche Pharma AG; 2026.
9. Rituximab [product information]. Grenzach-Wyhlen, Germany: Roche Pharma AG; 2025.