

Chronic Lymphocytic Leukemia

Research Updates for Patients

The Educated Patient[®]: Research Updates provides current clinical updates for different disease states. The following information is for educational purposes and is not medical advice.

FOR YOUR REFERENCE: What Are Clinical Trials?

Clinical trials determine whether a drug works in humans and whether it is safe and effective. For a drug to be approved for use, the Food and Drug Administration (FDA) requires four phases of a clinical trial. The number of participants increases in each phase, starting from 20 to 80 people for a phase 1 trial to up to several thousand for a phase 3 trial (Figure 1).¹

Phase 1: tests an experimental treatment on a small group of often healthy people to judge the drug's safety and side effects and find the correct dosage.

Phase 2: focuses on effectiveness and obtains preliminary data on whether the drug works in people who have a certain disease or condition.





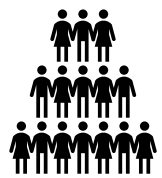
Phase 3: gathers more information about safety and effectiveness, studies different populations and dosages and examines the drug's use in combination with other drugs.

Phase 4: occurs after FDA approval; monitors safety and effectiveness in large, diverse populations; and collects information on long-term side effects.

FOR YOUR REFERENCE: What Is Chronic Lymphocytic Leukemia?

Chronic lymphocytic leukemia (CLL) is a form of cancer that starts in the blood-forming cells in bone marrow that become certain white blood cells, called **lymphocytes**. In CLL, cancer occurs in B cells, a type of lymphocyte, which defends your body against infection. These cells change and become cancer cells, or leukemia cells, that can grow out of control and spread by traveling in the blood to other parts of the body.²

Figure 1. Stages of Drug Development¹

		Clinical trials			After FDA approval
	Discovery and preclinical research	Phase 1	Phase 2	Phase 3	Phase 4
Clinical trial phase	Preclinical research is important to test whether the drug has the potential to cause serious harm to humans and decide whether the drug should be tested in people.	Phase 1 tests an experimental treatment on a small group of often healthy people to judge its safety and side effects and find the correct dosage.	Phase 2 focuses on effectiveness and obtains preliminary data on whether the drug works in people who have a certain disease or condition.	Phase 3 gathers more information about safety and effectiveness, studies different populations and dosages and examines use of the drug in combination with other drugs.	Phase 4 occurs after FDA approval; monitors safety and effectiveness in large, diverse populations; and collects information on long-term side effects. Also called postmarketing surveillance.
Participants	 <p>Drugs are tested in a lab setting (in cells and animals) to find possible beneficial effects against any number of diseases.</p>	 <p>Small group of healthy volunteers (typically 20-100 people)</p>	 <p>Small number of patients with the disease (typically several hundred)</p>	 <p>Large number of patients with the disease (typically a hundred to several thousand)</p>	 <p>Large, diverse populations</p>
Purpose	Discover new drugs, or develop existing drugs, that can potentially stop or reverse the effects of a disease	Identify how the investigational drug works, its safety and side effects	Determine efficacy within a specific population and short-term side effects and risks associated with the drug	Determine efficacy and safety, evaluate overall benefit and risk associated with the drug in patients with the disease	Learn more about the safety profile of the drug in a large population of patients treated with the drug after FDA approval

FDA, Food and Drug Administration.

Patients with CLL may experience symptoms such as weakness, fatigue, weight loss, chills, fever, night sweats, swollen lymph nodes, pain and a sense of fullness in the belly. Although these signs and symptoms can point to CLL, tests are needed for a diagnosis. Many people with CLL do not have any symptoms at the time of their diagnosis; their leukemia is found during blood tests for unrelated health issues or routine checkups.³ CLL is usually recognized when blood counts performed for unrelated reasons reveal lymphocytosis, or a higher-than-normal amount of lymphocytes in the body.

Treatment options for patients with CLL include the following⁴:

- Watchful waiting.
- Radiation therapy.
- Chemotherapy.
- Immunotherapy.
- Targeted therapy.
- Clinical trials.

Patients undergoing CLL treatment often experience a complete or partial response to initial therapy — but not always. Consequently, CLL can be classified as relapsed or refractory (R/R), depending on how the disease responds to treatment. Relapsed CLL describes CLL that responded to therapy initially but stopped responding after six or more months. CLL is called refractory if treatment does not result in the total disappearance of CLL cells (though the patient may have stable disease) or if the patient experiences worsening of CLL within six months of the last treatment.⁵

FOR YOUR REFERENCE:

What Agents Were Investigated in the UNITY-CLL Trial?

The combination of obinutuzumab and chlorambucil (a chemotherapy drug) is an established FDA-approved combination treatment for adults patients who have not had previous treatment for CLL.

Umbralisib and ublituximab are targeted drugs that are new and investigational treatments for CLL. These drugs affect mainly CLL cells and not normal cells in the body. They may work even if other treatment doesn't. They often come as pills that can be taken at home. These drugs have different, often less severe side effects than chemotherapy.

Umbralisib is a PI3K inhibitor that blocks a specific protein in B cells, called PI3K delta, that contributes to CLL and SLL growth. PI3K inhibitors may delay or prevent the growth of leukemia cells. Ukoniq also inhibits CK1-epsilon, which is a protein that helps CLL cancer cells survive, multiply and grow.⁶ It is FDA approved for other lymphoid malignancies that are relapsed or refractory after prior treatment (marginal zone lymphoma and follicular lymphoma).

Ublituximab is a monoclonal antibody, a type of protein involved in immune responses that attaches to CLL cells and causes them to die. This is an investigational drug that is administered intravenously, and it is shown to be well tolerated by patients and can be used alone or in combination with other agents.⁷

ASH 2020: Results From the UNITY-CLL Study of Ublituximab Doublet Versus Chemoimmunotherapy in CLL

In the phase 3 UNITY-CLL study, ublituximab in combination with Ukoniq (a combination referred to as U2) was evaluated in patients with treatment-naive or R/R CLL.⁸ In this study, the U2 combination worked better for the patients compared with chemoimmunotherapy, regardless of the patients' prior treatment.⁸

The study included 421 patients: 57% with treatment-naive CLL and 43% with R/R CLL. Patients received either U2 (210 patients) or obinutuzumab plus chlorambucil (211 patients).⁸

Efficacy Results

At a median follow-up of 37 months, U2 significantly prolonged progression-free survival (PFS; time without disease progression) compared with obinutuzumab plus chlorambucil (**Figure 2**).⁸ At the time of follow-up, treatment was ongoing for 77 patients (37%) with U2. These median PFS outcomes are provided below by subgroup⁸:

- **Total population:** 31.9 months in the U2 group versus 17.9 months in the obinutuzumab plus Chlorambucil group.
- **Treatment-naive patients (at the time of study enrollment):** 38.5 months in the U2 group versus 26.1 months in the obinutuzumab plus chlorambucil group.
- **Patients who received a median of two prior therapies:** 19.5 months in the U2 group versus 12.9 months in the obinutuzumab plus chlorambucil group.

Researchers also studied the patients' overall response rate (ORR) and complete response (CR). The ORR for the U2 group was 83% compared with 69% for the obinutuzumab plus chlorambucil group (**Figure 3**).⁸ Of the patients who responded to treatment, 5% achieved a CR or CR with incomplete marrow recovery with U2 versus 1% with the combination. More patients achieved a partial response in the U2 group than the obinutuzumab and chlorambucil group (79% vs. 67%).⁸

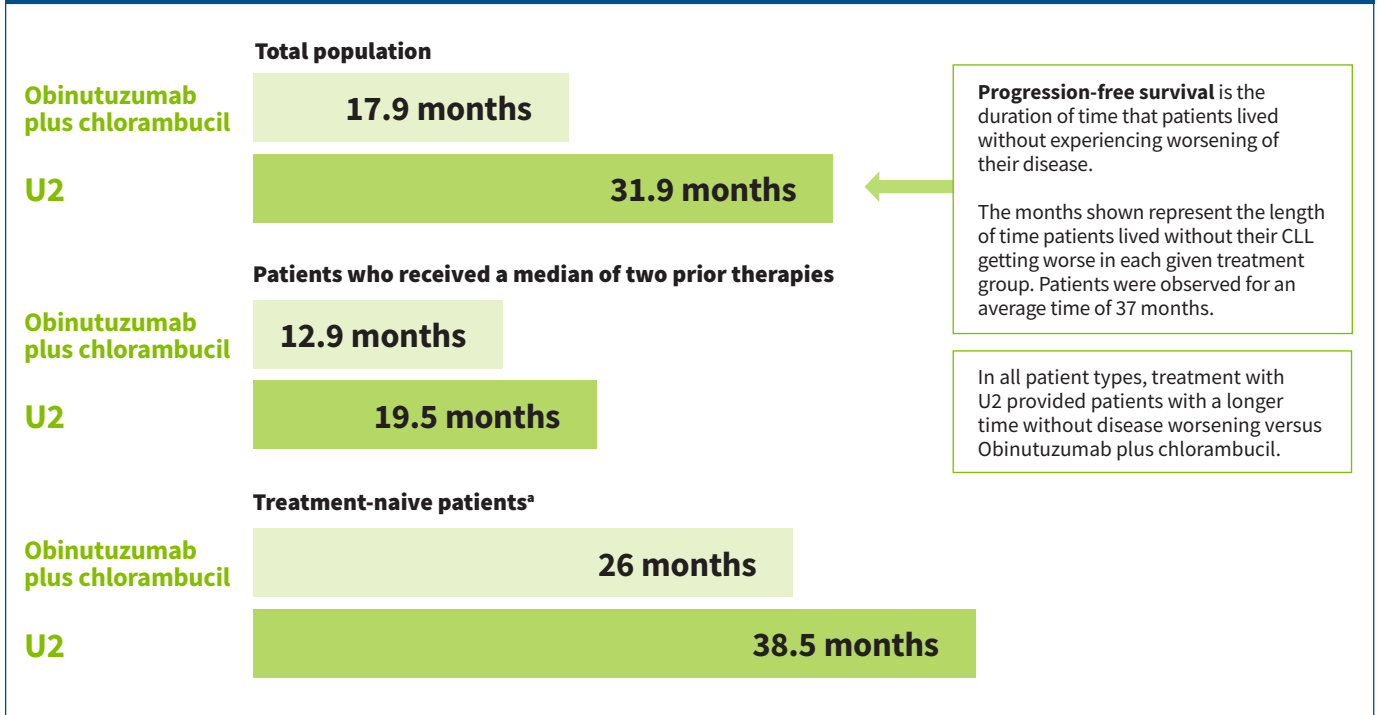
The ORRs were also higher in subgroup analyses in the U2 group compared with the obinutuzumab plus chlorambucil group⁸:

- Treatment-naive patients: 84% in the U2 group versus 78% in the obinutuzumab plus chlorambucil group.
- Previously treated patients: 82% in the U2 group versus 57% in the obinutuzumab plus chlorambucil group.
- Patients who had prior treatment with a Bruton tyrosine kinase inhibitor: 57% in the U2 group versus 25% in the obinutuzumab plus chlorambucil group.

Safety

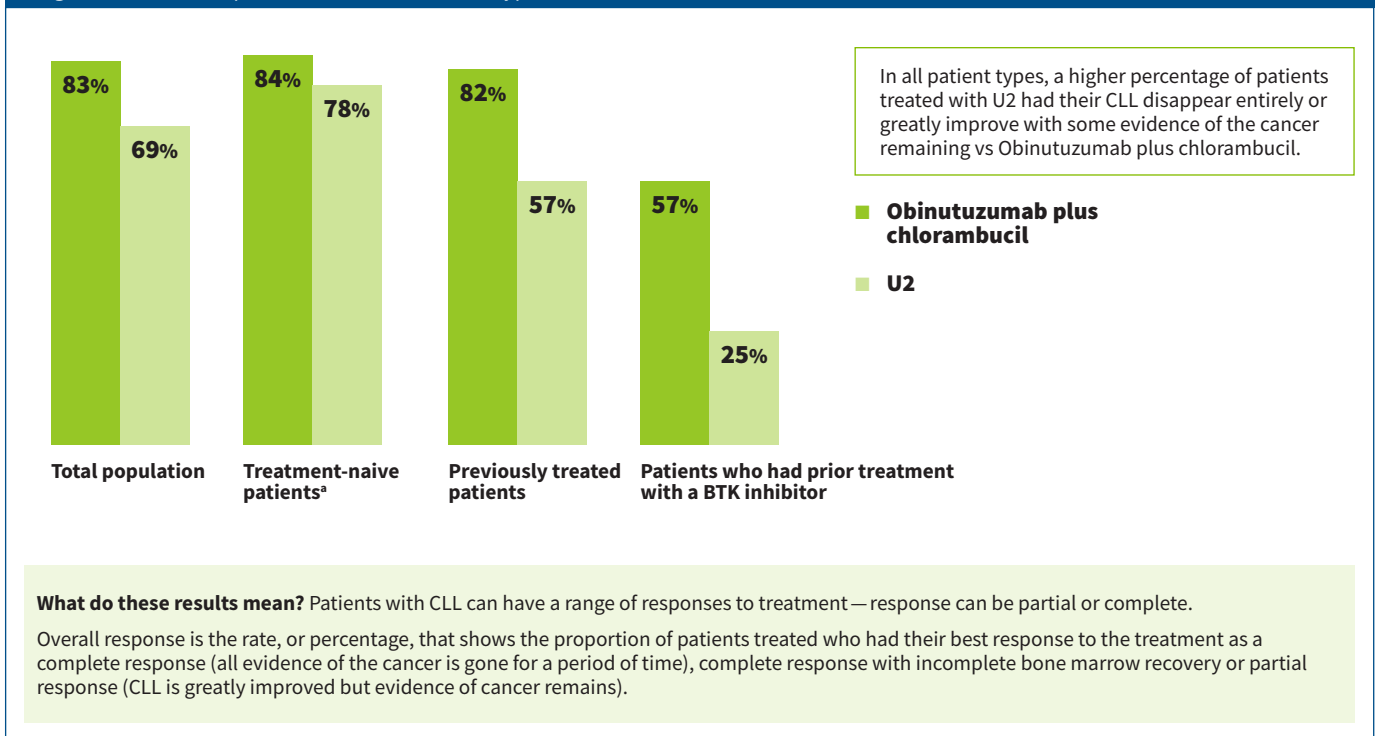
The safety of U2 was assessed from the first dose until 30 days after the last dose.⁸ Overall, the U2 regimen was associated with low rates of immune-mediated toxicities, including diarrhea, colitis, pneumonitis, and liver toxicity.^{8,9} Side effects led to treatment discontinuation in 35 patients (17%) in the U2 group and 16 patients (8%) in the obinutuzumab and chlorambucil group.⁸

Figure 2. U2 Improved Median Progression-Free Survival Across Patient Types⁸



CLL, chronic lymphocytic leukemia; U2, ublituximab in combination with umbralisib.
^aCLL that has not yet been treated with any agent.

Figure 3. Overall Response Rates Across Patient Types⁸



BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; U2, ublituximab in combination with umbralisib.
^aCLL that has not yet been treated with any agent.

The treatment-naïve patients experienced more frequent diarrhea than the patients who had prior therapy (13.8% vs. 10.0%). On the other hand, neutropenia (an abnormally low count of a type of white blood cell) was more frequent in patients who had prior therapy compared with the treatment-naïve patients (24.1% vs. 40.0%).⁸

Serious side effects of clinical interest that occurred at a higher rate with U2 than with obinutuzumab and chlorambucil, respectively, were⁸:

- Elevated liver enzyme levels
 - Alanine aminotransferase: 8.3% vs. 1.0%.
 - Aspartate aminotransferase: 5.3% vs. 2.0%.
- Colitis
 - Noninfectious colitis: 1.9% vs. 0%.
 - Infectious colitis: 0.5% vs. 0.5%.
- Pneumonitis: 0.5% vs. 0%.
- Rash: 2.4% vs. 0.5%.
- Opportunistic infections: 5.8% vs. 1.5%.

TG Therapeutics Inc has submitted a biologics license application with the FDA based on data from the UNITY-CLL study. The company plans to complete a new drug application submission for the U2 combination in CLL in 2021.¹⁰

Not all patients qualify for certain clinical trials. If you are interested in enrolling in a trial, talk to your doctor about which treatment options would be most appropriate for you.

FOR YOUR REFERENCE: Glossary of Terms¹⁻¹⁰

Alanine transaminase (ALT): an enzyme found in the liver that helps convert proteins into energy for the liver cells. When the liver is damaged, ALT is released into the bloodstream and levels increase.

Aspartate transaminase (AST): an enzyme that helps metabolize amino acids. Like ALT, AST is normally present in blood at low levels. An increase in AST levels may indicate liver damage, disease or muscle damage.

Bruton tyrosine kinase (BTK): a protein in B cells that sends signals, which help B cells survive and multiply

B cell: a type of white blood cell that is an important part of your immune system (the body's defense against infection)

Bone marrow: spongy tissue inside bones; cells that make blood cells are found in the bone marrow

Chemotherapy: treatment that uses drugs to stop the growth of cancer cells by either killing the cells or stopping them from dividing. These drugs are taken by mouth or injected and enter the bloodstream so they can help fight cancers that spread throughout the body (like CLL). This can affect cancer cells and normal cells.

Chronic lymphocytic leukemia (CLL): a slow-growing cancer in which too many immature lymphocytes (white blood cells) are found mostly in the blood and bone marrow

Clinical trial: a research study in which one or more human patients are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the intervention(s) on health-related biomedical or behavioral outcomes

Colitis: a condition marked by inflammation of the lining of the colon

Complete response (CR): the disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission.

Complete remission with incomplete count recovery (CRi): CR with incomplete blood count recovery

Efficacy: the ability of a therapy to produce the expected result under ideal circumstances

Gazyva (obinutuzumab): a type of antibody therapy that targets and attaches to the CD20 proteins found on follicular lymphoma cells. It may help a patient's immune system kill cancer cells or kill cancer cells directly. It can also harm healthy blood cells

Immunotherapy: type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection and other diseases. Some types of immunotherapy target only certain cells of the immune system. Others affect the immune system in a general way.

Leukemia: cancer that starts in blood-forming tissue, such as bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the bloodstream

Liver enzymes: certain enzymes and proteins in your blood. Levels that are higher or lower than normal may indicate liver problems. ALT and AST are examples of liver enzymes that are tested

Lymphocytes: a type of white blood cell that is made in the bone marrow and found in the blood and lymph tissue

Opportunistic infections: infections that occur more frequently in people with weakened immune systems

Overall response rate (ORR): the percentage of people in a study or treatment group who have a partial or complete response to the treatment within a certain period of time

Partial response: a decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment. Also called partial remission.

Phase 1: trial that tests an experimental treatment on a small group of often healthy people to judge its safety and side effects and to find the correct drug dosage

Phase 2: trial that focuses primarily on effectiveness of drug and obtains preliminary data on whether it works in people who have a certain disease or condition

Phase 3: trial that gathers more information about safety and effectiveness, studies different populations and different dosages and examines use of the drug in combination with other drugs

Phase 4: trial that occurs after FDA approval; monitors safety and effectiveness in large, diverse populations; and collects information on long-term side effects

PI3K inhibitor: a targeted therapy that works by blocking a specific protein in B cells, called PI3K delta, that contributes to CLL and SLL growth. PI3K inhibitors may delay or prevent the growth of leukemia cells

Pneumonitis: a condition marked by inflammation of lung tissue

Progression-free survival: the length of time during and after the treatment of a disease that a patient lives with the disease but it does not get worse

Radiation therapy: type of cancer treatment that uses beams of intense energy to kill cancer cells

Refractory: a disease state or condition that does not respond to treatment or medication. Refers to when the lymphoma does not respond to treatment (the cancer cells continue to grow) or when the response to treatment does not last very long.

Relapsed: a return of signs and symptoms of cancer after undergoing treatment and/or taking medication. Relapsed is the disease that returns or grows again after a period of remission following one or more treatments. Marked by an initial response to treatment that is no longer present after six months or more

Side effect: An unintended reaction to, or result of, a treatment

Small lymphocytic lymphoma (SLL): a slow-growing type of lymphoma in which too many immature lymphocytes (white blood cells) are found mostly in the lymph nodes

Targeted therapy: a cancer treatment that uses drugs to target specific aspects of the cancer cells

Treatment-naïve CLL: disease that has not yet been treated with any agent

Ukoniq (umbralisib): an FDA-approved oral PI3K inhibitor indicated for the treatment of adult patients with R/R marginal zone lymphoma who have received at least one prior anti-CD20 based regimen and adult patients with R/R follicular lymphoma who have received at least three prior lines of systemic therapy

Ublituximab: a type of antibody therapy IgG1 monoclonal antibody that targets and attaches to the CD20 proteins on CLL cells to kill them

Watchful waiting: a strategy in which treatment is not started right away; instead, symptoms are observed and time is allowed to pass before medical intervention or therapy is used

White blood cell: a type of cell that is found in the blood and lymph tissue that helps fight infections and other diseases. Lymphocytes (T and B cells) are types of white blood cells.

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