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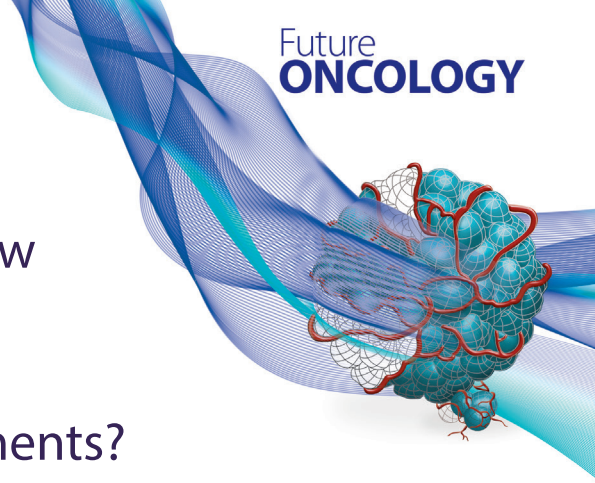

Future ONCOLOGY

How well does acalabrutinib work and how safe is it to treat patients with chronic lymphocytic leukemia/small lymphocytic lymphoma who have had previous treatments? a plain language summary of 2 key studies

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Where can I find the original articles on which this summary is based?

The original article, 'Acalabrutinib Versus Investigator's Choice in Relapsed/Refractory Chronic Lymphocytic Leukemia: Final ASCEND Trial Results,' is free to access at: https://journals.lww.com/hemasphere/fulltext/2022/12000/acalabrutinib_versus_investigator_s_choice_in.4.aspx.

The original article, 'Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial,' is free to access at: https://ascopubs.org/doi/pdf/10.1200/JCO.21.01210.

Summary

What is this summary about?

This summary is about acalabrutinib, a medication available for the treatment of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), which are types of blood cancer. We selected 2 key studies (ELEVATE-RR and ASCEND) that will provide important information about acalabrutinib for patients with CLL/SLL who had received other treatments in the past for their blood cancer. In these publications, acalabrutinib is compared with standard treatments, such as chemotherapy, or to more modern targeted therapies.

What were the results?

The first study (ASCEND) included patients with CLL/SLL who were not responding to prior treatment ('refractory') or those who initially responded to treatment but the disease had returned or worsened ('relapsed'). The results showed that more patients treated in this study with acalabrutinib (62%) were alive without worsening of their disease compared with those receiving idelalisib plus rituximab (23%) or bendamustine plus rituximab (5%), a targeted therapy and a chemoimmunotherapy medication, respectively.

How to say (download PDF and double click sound icon to play sound)...

- **Acalabrutinib:** uh-KA-luh-BROO-tih-nib
- **Lymphocytic Leukemia:** LIM-foh-SIH-tik loo-KEE-mee-uh
- **Lymphocytic Lymphoma:** LIM-foh-SIH-tik lim-FOH-muh
- **Idelalisib:** Eye-deh-luh-LIH-sib
- **Rituximab:** rih-TUK-sih-mab
- **Anemia:** uh-NEE-mee-uh
- **Thrombocytopenia:** throm-bow-sai-tuh-PEE-nee-uh
- **Neutropenia:** nyoo-truh-PEE-nee-uh
- **Bendamustine:** ben-duh-MUH-steen
- **Immunotherapy:** i-myoo-no-THEH-ruh-pee
- **Cytometry:** sai-TAA-muh-tree
- **Bruton tyrosine kinase:** broo-tuhn TAI-ruh-seen KAI-nays

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The second study (ELEVATE-RR) also included people with CLL/SLL with high-risk features (that is, **del(17p)/*TP53*** and **del(11q)**) and previous unsuccessful therapies (who either relapsed or were refractory). This study showed that treatment with acalabrutinib was similar to ibrutinib (another targeted therapy with similar features) in effectiveness and caused fewer side effects (an unwanted and sometimes dangerous reaction caused by a medication) affecting the heart rhythm, blood pressure, and bleeding.

del(17p), *TP53*, and del(11q): Different types of mistakes in genes that increase the risk of poor outcomes among patients with CLL.

What do the results mean?
These results mean that acalabrutinib is an effective and safe option for patients with CLL/SLL who have had unsuccessful treatments in the past, including those who relapsed or were refractory or with high-risk features.

What is the purpose of this plain language summary?

The purpose of this plain language summary is to help you to understand the findings from recent research. The results of these studies may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence.

Who should read this article?

This article can help patients, healthcare providers, caregivers, and patient advocates understand more about treatment options for CLL/SLL, which are types of blood cancer. Healthcare providers, such as doctors, pharmacists, nurses, nurse practitioners, and physician assistants can use this summary to present the study results to their patients in an understandable manner and help them make an informed decision about their treatments.

Who sponsored this study?

These studies were **sponsored** by AstraZeneca.

Sponsor: A company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information from the study.

Why have we made this PLSP?

This plain language summary looks at two studies that used acalabrutinib to treat patients with relapsed or refractory CLL/SLL. The goal of this plain language summary is to help people affected by CLL/SLL and their healthcare providers to understand the results of these studies.

Before discussing these studies, it will be important to have some understanding about the disease and acalabrutinib – the treatment we will be discussing.

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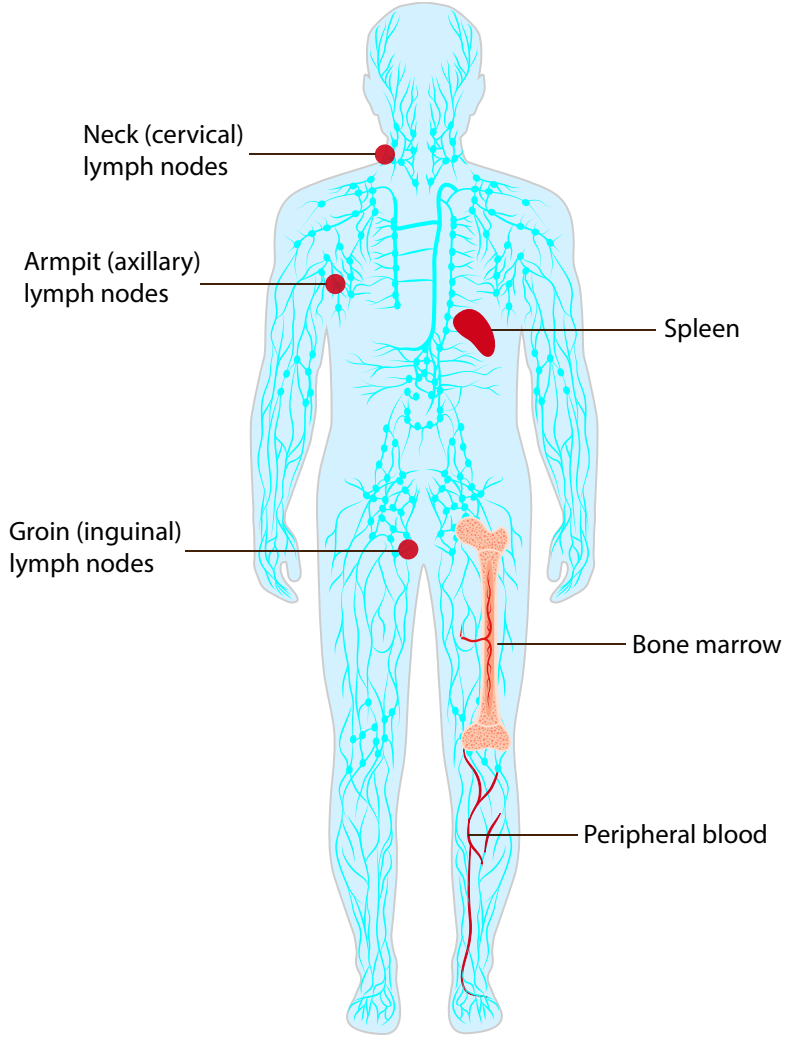
What is chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)?

CLL is one of the most common types of leukemia (or blood cancer in adults, with approximately 4 new cases per 100,000 people diagnosed every year in Western countries. The exact cause of CLL is not known, although increased risk has been associated with older age, male sex, genetic factors, and certain ethnicities. There also may be an increased risk of CLL with excessive chemical exposure, such as in military veterans who served in Vietnam (for example, Agent Orange) or the Middle East (for example, Desert Storm, where burn pits were common and soldiers were exposed to multiple chemicals). Research has shown that CLL cells have several **genetic mutations** or mistakes that make them live longer and divide faster than normal cells.

Genetic mutations: An alteration in the DNA material (the instruction book of cells) that controls how a person's cells work, how they divide, and how it affects the body. In some instances, mutations can be harmful and cause disease.

Most people are between 64 and 75 years of age when they are diagnosed with CLL, although the disease can affect younger and older people. There are more cases of CLL among Whites than Blacks or Asians, and men are 2 times more likely to have the disease than women.

Although both diseases are the result of an abnormal production of B cells, they behave in different ways depending on where those cells mainly grow.



Median age (**70 years**)

Affects **Whites more frequently** than Blacks or Asians

Affects **men twice as much** as women

In people with CLL, the abnormal cells are found mostly in the **peripheral blood** and the **bone marrow**. However, people with CLL can have enlarged lymph nodes as well. In people with SLL, the cancer cells tend to appear in the lymph nodes of the **lymphatic system**, causing painless swellings in the neck, armpits, and groin.

Patients with CLL are usually studied alongside patients with SLL, as CLL and SLL are different forms of the same disease. The main characteristic of these slow-growing cancers is an excessive production of abnormal lymphocytes, a type of white blood cell that helps the immune system, or the body's natural defense system, fight against foreign invaders such as viruses and bacteria or abnormal cells such as cancer cells.

Peripheral blood: Blood that is circulating throughout the body (for example, in arteries and veins); this is different from blood enclosed in the liver, spleen, bone marrow, and lymphatic system.

Bone marrow: The spongy tissue found in the center of most bones; it contains stem cells (special cells that can develop into many different types of cells), including those that generate red blood cells, white blood cells, and blood platelets.

Lymphatic system: All the tissues and organs that produce, store, and carry the white blood cells that fight infections and other diseases.

3 main types of **lymphocytes**

B lymphocytes (B cells), which produce antibodies, a type of protein that helps the body to fight infections

T lymphocytes (T cells), which help B cells produce antibodies, eliminate cancer cells, and directly kill infectious agents

Natural killer cells (NK cells), which attack and kill viruses and cancer cells

Three types of lymphocytes are part of the immune system: B lymphocytes (B cells), which produce antibodies to help the body fight infections; T lymphocytes (T cells), which help B cells produce antibodies and directly kill infectious agents; and natural killer cells (NK cells), which attack and kill viruses and cancer cells. When a person has CLL/SLL, the body produces abnormal B cells that are not efficient in fighting infections and block the other normal lymphocytes (NK cells and T cells) from doing their jobs properly.

Most people with CLL/SLL do not have any signs or symptoms at time of first diagnosis, and the disease is usually discovered through a routine blood test done for other reasons. As the production of abnormal B cells increases and the disease worsens, patients may start experiencing fatigue (extreme tiredness), unexplained weight loss, decreased ability to eat a full meal, infections, fever, drenching night sweats, easy bleeding or bruising, a sensation of fullness below the ribs, and flu-like symptoms. However, signs and symptoms can vary significantly from person to person, and the vast majority of individuals show no symptoms at the time of diagnosis. People can also present with enlarged lymph nodes; these can be detected by chance during imaging procedures (such as computed tomography [CT] or magnetic resonance imaging [MRI] scans) or they can just be felt by the doctor during a routine examination or by chance by the patients themselves. Lymph nodes are bean-shaped structures found throughout the body that help filter the fluid traveling through the immune system.

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How is CLL/SLL diagnosed?

To make a diagnosis, the physician will start by taking the patient's history and performing a complete physical examination, followed by specialized laboratory tests (**complete blood count**, peripheral blood smear, **flow cytometry**) and, if necessary, imaging tests, like ultrasound or CT. Additional tests may be used prior to starting initial therapy to help select appropriate treatment (for example, **interphase cytogenetics**, **beta-2 microglobulin** level [B2M], **IGHV mutational testing, and sequencing for *TP53* mutations**). These tests would not necessarily be repeated prior to starting treatment of relapsed or refractory disease. Many of these tests are not required and may or may not be offered.

Complete blood count: A blood test to measure the number of various types of cells in the blood to identify any unusual increases or decreases.

Flow cytometry: A specialized test to characterize and count different types of cells, such as from a blood sample.

Interphase cytogenetics: A test to look at genes and chromosomes in order to detect various types of chromosomal abnormalities, such as deletions (when parts of genes are missing).

Beta-2 microglobulin: A protein found on the surface of cells that can indicate the presence of certain types of cancer.

IGHV mutational testing, sequencing for *TP53* mutations: Tests to determine the presence of genetic mutations that are linked to poor outcomes among patients with CLL.

What types of treatment are available for CLL/SLL?

Most patients diagnosed with CLL will not need immediate treatment. In fact, some may never need treatment. Since CLL can progress slowly and most patients are asymptomatic at the time of diagnosis, physicians may propose a 'watch and wait' or active surveillance strategy, closely monitoring the individual for any signs of the disease getting worse before starting an active treatment.

When it's time to start the treatment, there are several options available, and the choice of therapy will depend on many factors, like the patient's age and fitness, the type of genetic mutations detected on blood tests, and in the case of those with **relapsed** or **refractory disease**, which treatment they received before. Response to therapy can vary considerably from patient to patient.

Relapsed disease: The disease returns following a period of improvement with treatment.

Refractory disease: The disease does not respond to initial treatment or becomes resistant during treatment.

Monoclonal antibody: A type of treatment that targets specific proteins on the surface of cancer cells to be killed by the immune system.

There are several types of medications available for the treatment of CLL/SLL:

Targeted therapies: These medications block specific parts (proteins) on the surface or inside the cancer cell. When the proteins are blocked, the cancer cells die or stop multiplying. Targeted therapies are a new type of medication that were developed in the last 10 years.

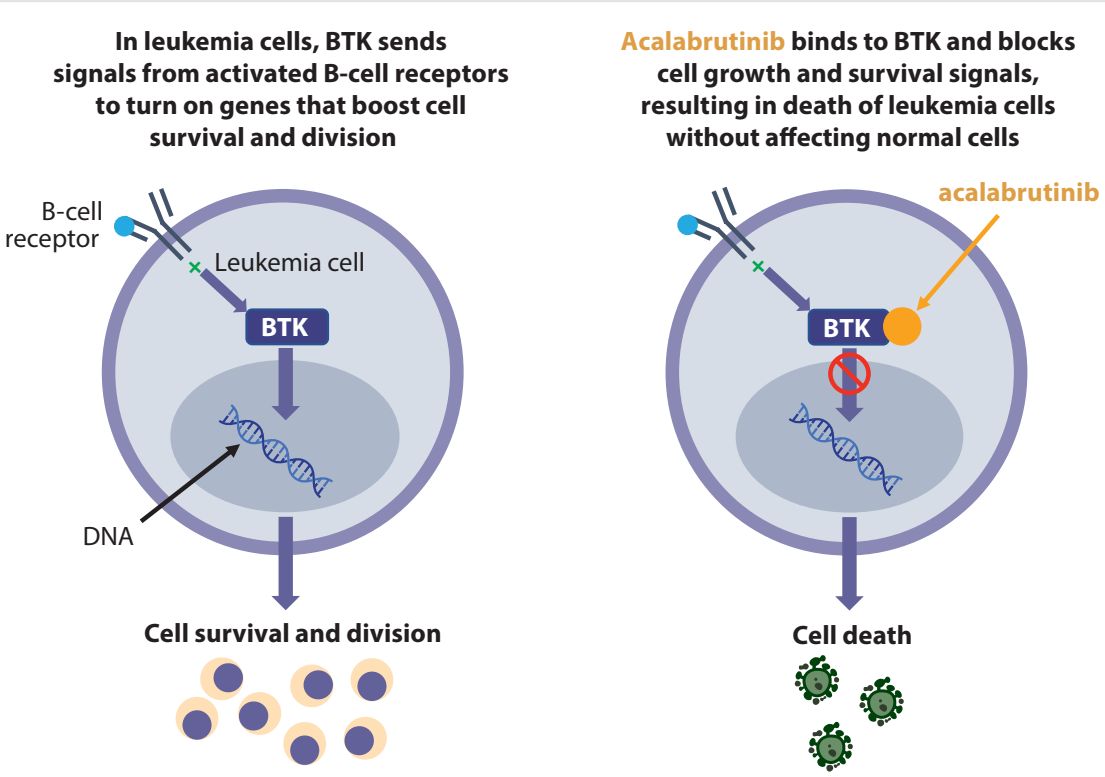
Immunotherapy: These drugs help the immune system to kill cancer cells. **Monoclonal antibodies** are a type of immunotherapy used to treat CLL/SLL. They attach to specific proteins on the surface of the cancer cells, marking the cells so that the immune system can recognize and destroy them.

Chemotherapy agents: These drugs either kill cancer cells or stop them from multiplying. However, chemotherapy can also affect healthy cells that divide quickly and cause unwanted effects.

What is acalabrutinib?

Acalabrutinib is a targeted therapy. It is a therapy taken by mouth (oral) approved by the United States Food and Drug Administration (FDA) and in the European Union for the treatment of some cancers that occur in B cells, including CLL and SLL. B cells contain a protein called Bruton tyrosine kinase (BTK) that can boost the growth and survival of cancer cells. Abnormal B-cell signaling plays a role in B-cell cancers (see illustration below).

Acalabrutinib is a 'BTK inhibitor' which means that it works by blocking a specific function of BTK and stops the cancer cells from growing and causes them to die. Acalabrutinib specifically targets the BTK protein and may reduce the chance of unwanted side effects seen with an older BTK inhibitor, such as irregular or rapid heartbeats, high blood pressure, and bleeding.



Now, let's take a look at the selected studies

ASCEND study – compared acalabrutinib to physician's choice of idelalisib plus rituximab (or bendamustine plus rituximab)

Who participated in this study and how were they treated?

This study included 310 patients from around the world (including Europe, North America, Asia, and Australia) with CLL who had relapsed or refractory disease. Patients were allowed to participate in the study if they were 18 years or older, had at least one prior treatment for CLL, and were able to walk and care for themselves. The study was 'randomized,' which means that patients are randomly (by chance) divided into separate groups to compare different treatments. This random assignment of patients into groups increases the likelihood that the groups will be more even regarding certain characteristics (for example, age, sex, genetic mutations, extent of disease).

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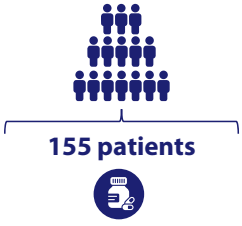
When the groups are more even in terms of these characteristics, the effects of the treatments studied can be compared with one another more fairly.

Cycles: Pre-determined periods to mark the time on treatment. For this study, every 4 weeks was considered as 1 cycle of treatment.

Patients were divided into 2 groups. In group 1, patients received acalabrutinib 1 tablet, twice a day, every day until there were either signs of disease worsening or unacceptable side effects. In group 2, the patient's physician could choose between 2 treatments ('physician's choice'): idelalisib (a targeted medication that blocks a protein called PI3K in normal and cancerous B cells) plus rituximab (a medication that attaches itself to the CD20 protein on the surface of some B cells, including cancerous B cells, helping the immune system attack and kill them) or bendamustine (a chemotherapy that kills cancer cells by damaging their genetic material or DNA) plus rituximab. This was an open-label study, meaning the investigators and patients knew which medications were being given to each patient. Patients receiving physician's choice of therapy who experienced worsening of disease were allowed to switch to acalabrutinib therapy.

Group 1:



155 patients

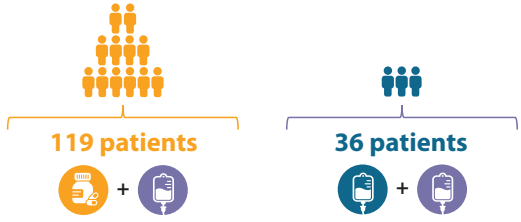
63% 65 years or older | **70%** were men | **30%** were women

- Patients in this group had received a median (the middle value in a set of numbers) of 1 treatment before entering the study (ranging from 1 up to 8 previous treatments).
- 1 patient in group 1 was randomized but did not receive treatment.

acalabrutinib

154 patients took 1 tablet, twice a day (about 12 hours apart), every day until there were either signs of disease worsening or unacceptable side effects.

Group 2:



119 patients | **36 patients**

63% 65 years or older | **65%** were men | **35%** were women

- Patients in this group had received a median of 2 treatments before entering the study (ranging from 1 up to 10 previous treatments).
- 2 patients in group 2 were randomized but did not receive treatment.

idelalisib + **rituximab**

118 patients took **idelalisib** 1 pill, twice daily, every day by mouth until there were either signs of disease worsening or unacceptable side effects. They also were given **rituximab** directly into the vein, at pre-determined intervals for a total of 8 doses.

bendamustine + **rituximab**

35 patients were given **bendamustine** infusions (or given into the vein) on days 1 and 2 for 6 **cycles**.

Rituximab was given directly into the vein, at pre-determined intervals for a total of 8 doses.

This study started in February 2017 and the patients were monitored for 4 years.

What were the researchers looking for?

The main questions the researchers asked were:

- How long did the patients with relapsed/refractory CLL/SLL who received acalabrutinib treatment live without their disease getting worse compared with those who received their physician's choice of treatment (idelalisib plus rituximab or bendamustine plus rituximab)? This is known as progression-free survival.
- Overall, how many patients were alive at the last time the results were analyzed?
- How many patients in each group had their cancer respond positively to the treatment (complete remission [when all signs and symptoms of cancer disappear], partial remission, manageable side effects)?

To evaluate whether a patient is responding to the treatment, the physician performed a physical examination, blood tests, bone marrow biopsy (when a small sample of cells are removed for analysis), and sometimes imaging tests such as tomography.

When a patient is in complete remission:

- Their lymph nodes are normal in size (1.5 centimeters or smaller) during physical examination
- The spleen and liver are of a normal size
- Blood tests show normal or near normal levels of lymphocytes, platelets, and hemoglobin (parts of blood)
- There are no CLL cells in the bone marrow, and the patient does not have systemic (affecting the whole body) or general symptoms (fever, night sweats, weight loss, or extreme fatigue [presence of mild to moderate fatigue does not necessarily indicate failure to respond])

In a case of partial remission, some signs of the disease persist, but the patient has an improvement in at least 2 main items:

- A decrease of at least 50% in the size of the lymph nodes, liver, or spleen compared with before the treatment
- A reduction of at least 50% in the number of lymphocytes in the blood tests

Patients may still have CLL in their bone marrow and present with general symptoms.

The physicians also asked:

- What were the side effects that happened during treatment?
- How many patients had to have their medication dosage reduced or had to discontinue treatment because of side effects?

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What were the results of this study?

How long did the patients live without the disease getting worse?
The 42-month progression-free survival rates were:

62% of patients treated with acalabrutinib

23% of patients treated with idelalisib + rituximab

5% of patients treated with bendamustine + rituximab

In how many patients did the disease respond positively to the treatments in each group?

83% of patients treated with acalabrutinib

84% of patients treated with idelalisib plus rituximab or bendamustine plus rituximab

How many patients were alive at the last time the results were analyzed?
The 42-month overall survival rates were:

78% of patients treated with acalabrutinib

65% of patients treated with idelalisib plus rituximab or bendamustine plus rituximab

What were the side effects from the treatments?
The most common side effects of any severity affecting at least 20% of patients differed in each group:

Patients treated with acalabrutinib

Neutropenia

24% of patients

Headache

23% of patients

Diarrhea (loose or watery poo)

21% of patients

Upper respiratory tract infection

20% of patients

Patients treated with bendamustine plus rituximab

Neutropenia

34% of patients

Fatigue (extreme tiredness)

23% of patients

Reaction to the infusion

23% of patients

Nausea (feeling sick)

20% of patients

Patients treated with idelalisib plus rituximab

Diarrhea

53% of patients

Neutropenia

47% of patients

Neutropenia: A decrease in the number of a subset of white blood cells that help your body fight infections.

Upper respiratory tract infection: An infection of the nose, throat, or windpipe.

- Most side effects do not persist for the duration of therapy.
- Other side effects include pneumonia, cough, fever, and body aches, but they occurred in less than 20% of patients.

How many patients required reduction in the treatment dose because of side effects?
Side effects that required reduction in the dose of medication were observed in:


6% of patients treated with acalabrutinib


12% of patients treated with idelalisib + rituximab


14% of patients treated with bendamustine + rituximab

What do the results of this study mean?

After approximately 4 years of monitoring, the physicians concluded that:

- Acalabrutinib was an effective and safe treatment for people with CLL/SLL who had been treated for their disease before.
- More patients who received acalabrutinib were likely to be alive without worsening of disease compared with those who received their physician's choice of treatment (idelalisib plus rituximab or bendamustine plus rituximab).
- Fewer patients receiving acalabrutinib had to have the dose of their medication reduced because of side effects compared with those treated with idelalisib plus rituximab or bendamustine plus rituximab.
- The ability to see differences in overall survival between treatments was limited by a high percentage of patients who switched from physician's choice therapy to acalabrutinib.

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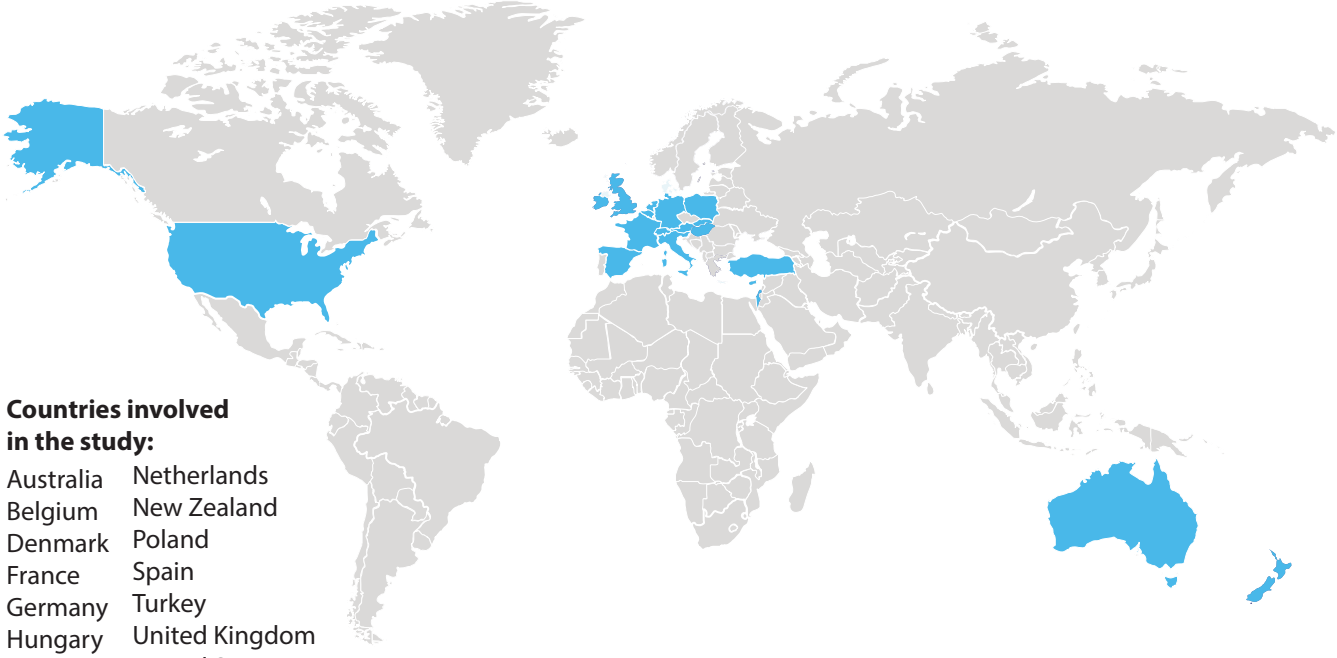
ELEVATE-RR study – compared acalabrutinib with a similar targeted therapy (ibrutinib)

Who participated in this study and how were they treated?

This randomized, open-label study took place in 124 centers in 15 countries and included 533 patients with CLL who had been treated for their leukemia in the past.

Patients were allowed to participate in the study if they were 18 years or older, had at least one prior treatment for CLL, were able to walk and care for themselves, and did not have significant cardiovascular disease or use certain medication (such as warfarin or a proton pump inhibitor). All patients included in the study had at least 1 high-risk chromosomal abnormality that increased their chance of having a worse response to chemotherapy than people without the abnormality.



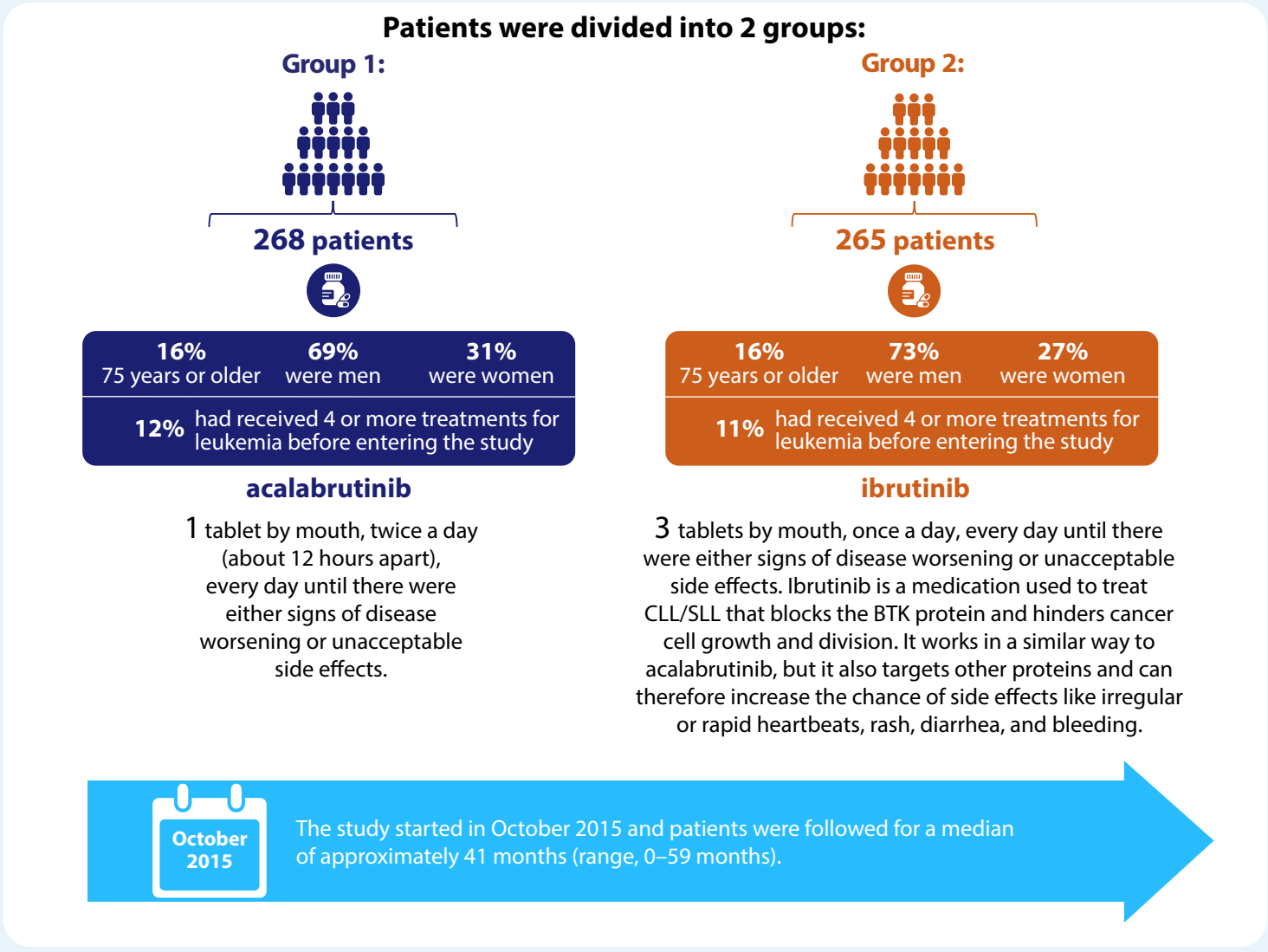
Countries involved in the study:

Australia
Belgium
Denmark
France
Germany
Hungary
Israel
Italy
Netherlands
New Zealand
Poland
Spain
Turkey
United Kingdom
United States

124 centers

15 countries

533 patients



What were the physicians looking for?

The physicians wanted to find out if acalabrutinib was at least as effective as ibrutinib when treating people with CLL/SLL who had failed previous treatments. A non-inferiority study is designed to discover if one product is no worse in terms of efficacy or safety than the other drug to which it is being compared. Non-inferiority studies are useful when you cannot use a placebo (inactive treatment) as a comparator.

The physicians also wanted to know:

- How long did the patients with CLL/SLL who received acalabrutinib live without their disease getting worse compared with those receiving ibrutinib?
- How many patients experienced a positive response to the treatment (complete remission or partial remission)?
- What side effects happened during treatment, especially those related to irregular or rapid heartbeats?

To evaluate whether a patient is responding to treatment, the physician performed a physical examination, blood tests, bone marrow biopsy, and sometimes imaging tests such as tomography. Refer to page 8 to read about how complete remission and partial remission are evaluated.

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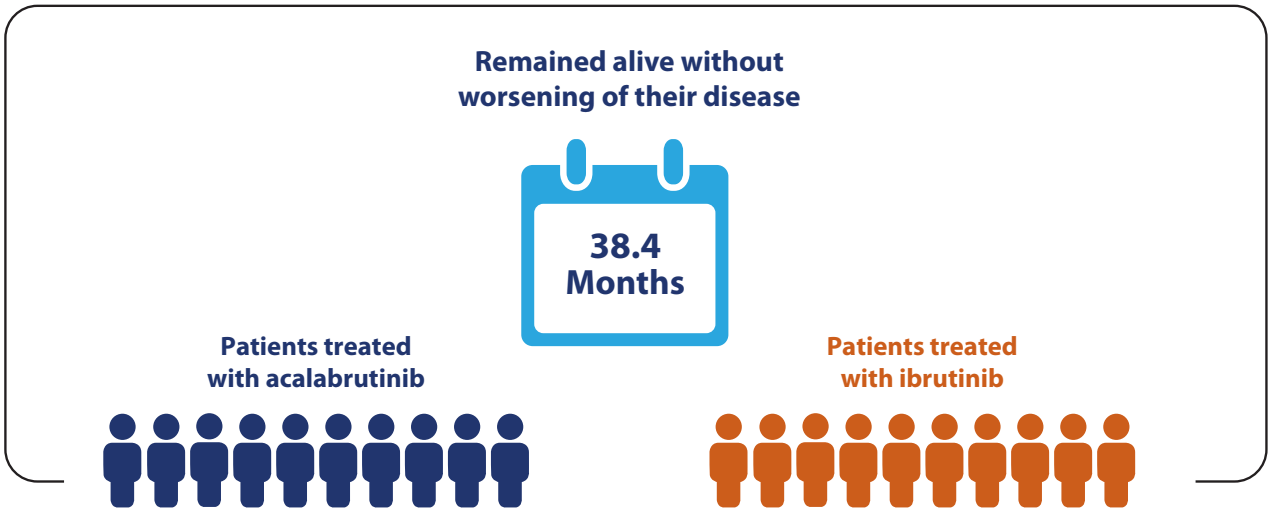
What were the results of this study?

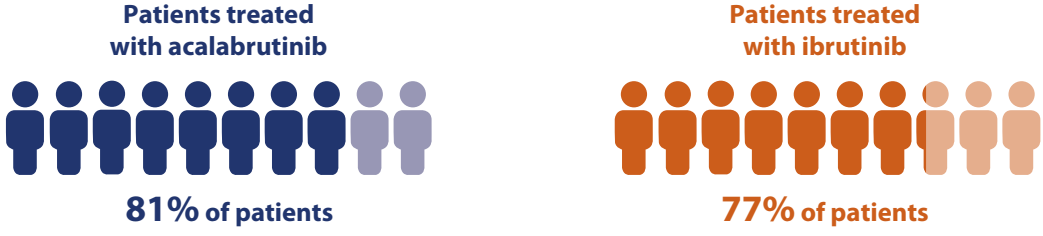
How long did patients in each group stay alive without worsening of the disease?

The median time for patients who remained alive without worsening of their disease was comparable between study groups.



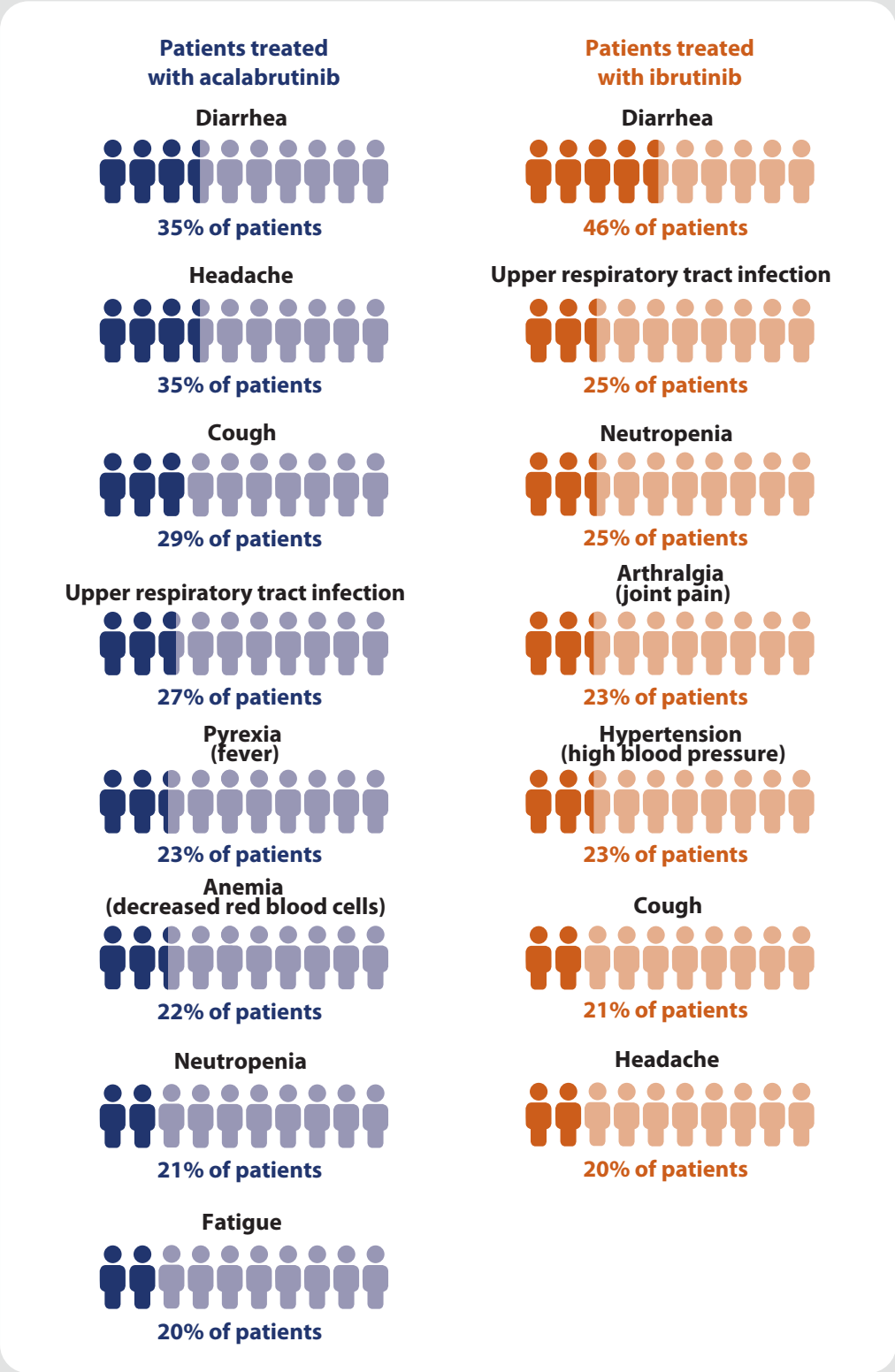
In how many patients did the disease respond positively to the treatments in each group?

81% of the patients treated with acalabrutinib and 77% of those treated with ibrutinib showed positive responses (complete or partial) to the treatments when assessed by independent reviewers.



What were the side effects from the treatments?

Overall, the most common side effects of any severity affecting 20% or more of patients in each group were:



- The proportions of patients with severe side effects that interfered with their daily lives, required hospitalization, or were life-threatening were similar in both groups: acalabrutinib (31%) and ibrutinib (30%).
- Fewer patients (39 patients [15%]) receiving acalabrutinib had to stop their treatment because of side effects than those treated with ibrutinib (56 patients [21%]).
- Fewer patients (25 patients [9%]) receiving acalabrutinib had irregular or rapid heartbeats of any severity compared with those treated with ibrutinib (42 patients [16%]).
- Most side effects did not persist for the duration of treatment.

What do the results of this study mean?

- Treatment with acalabrutinib was at least as effective as ibrutinib for people with CLL/SLL who have had previous therapy for their disease.
- Acalabrutinib is better tolerated than ibrutinib, with fewer side effects of irregular or rapid heartbeats and fewer treatment discontinuations when compared to ibrutinib.

Disclosure statement

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