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Plain Language Summary of Publication

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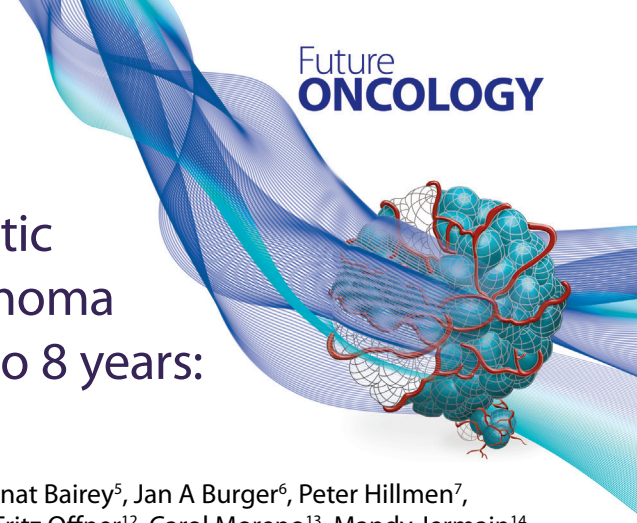

Many people with chronic lymphocytic leukemia or small lymphocytic lymphoma benefit from ibrutinib treatment up to 8 years: a plain language summary

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Summary

What is this summary about?
This is a plain language summary of a publication describing long-term results from the RESONATE-2 study with up to 8 years of follow-up. The original paper was published in *Blood Advances* in June 2022.

What were the results?
Researchers looked at 269 adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who had not received any treatment for their CLL/SLL. Study participants were randomly divided into two groups: 136 participants received treatment with a drug called ibrutinib, and 133 participants received treatment with a drug called chlorambucil. Participants in the study were treated and followed for up to 8 years, with results showing that more participants who took ibrutinib (59%) were alive without worsening of their disease at 7 years after starting treatment than participants who took chlorambucil (9%). Almost half of the participants (42%) were able to stay on ibrutinib treatment for up to 8 years.

What do the results of the study mean?
In people with CLL or SLL, more participants who were taking ibrutinib were alive without worsening of their disease after 7 years compared with participants who took chlorambucil.

How to say (double-click on the icon to play sound)…

- **Ibrutinib:** eye-BREW-tin-ib
- **Chlorambucil:** klor-AM-byoo-sil
- **Chronic lymphocytic leukemia:** KRAH-nik LIM-foh-SIH-tik loo-KEE-mee-uh
- **Small lymphocytic lymphoma:** smAHl LIM-foh-SIH-tik lim-FOH-muh

Who is this article for?

This summary may be helpful for people with CLL/SLL and their family members or caregivers. Patient advocates and healthcare professionals searching for treatment options for patients may also find this information useful.

Where can you find the original article on which this summary is based?

You can read the full article called 'Up to 8 Years Follow-up From RESONATE-2: First-Line Ibrutinib Treatment for Patients With Chronic Lymphocytic Leukemia' published in *Blood Advances* for free at: https://doi.org/10.1182/bloodadvances.2021006434.

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What are CLL and SLL?

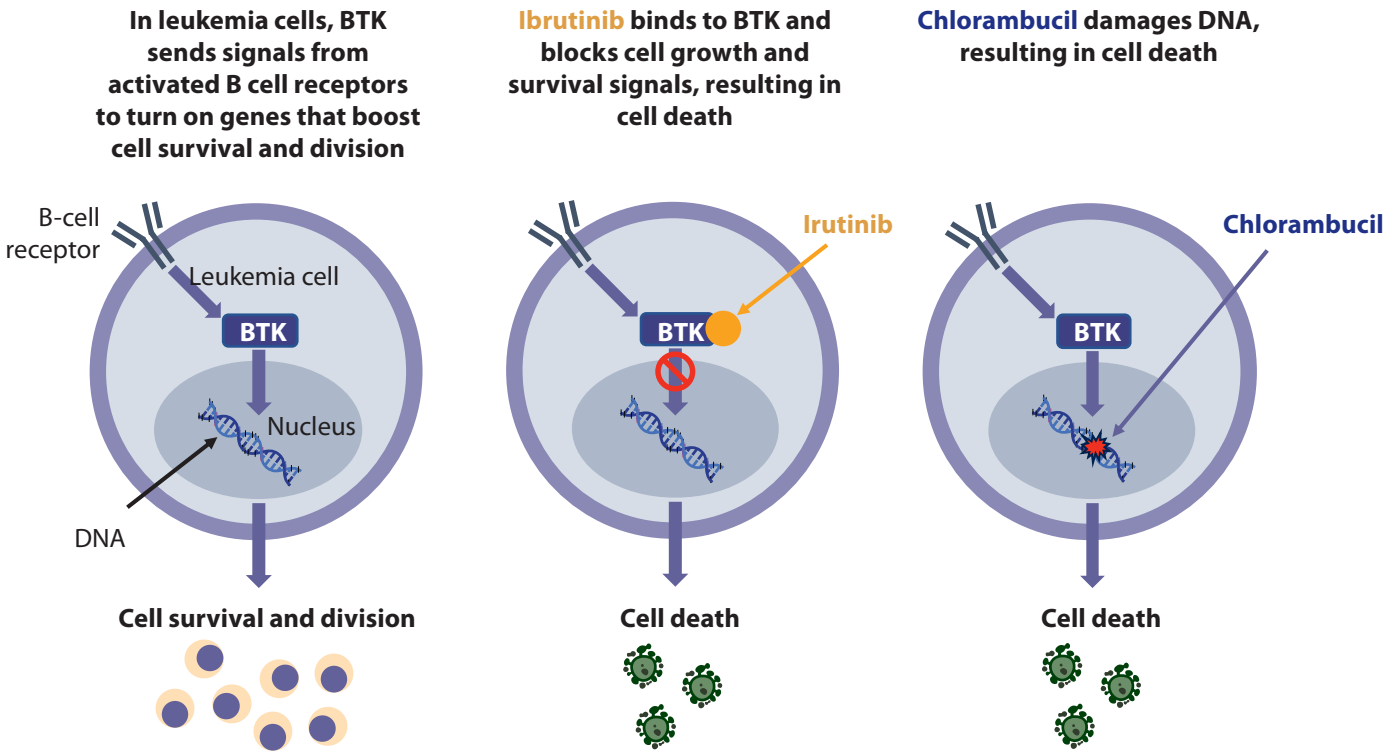
- LL and SLL are essentially the same type of cancer that affects a kind of white blood cells called **B-lymphocytes**.
- B-lymphocytes start developing in the **bone marrow** and then move to other organs of the immune system, such as the **lymph nodes** and **spleen**, where they develop into mature B-lymphocytes.
- When B-lymphocytes become abnormal (cancerous), they can build up and outnumber healthy blood cells.
- The cancer is called CLL if the cancer cells (also known as leukemia cells) are mostly found in the blood and bone marrow and SLL if leukemia cells are mostly found in the lymph nodes.
- In CLL and SLL, the leukemia cells often build up slowly over many months or years.

B-lymphocyte: A type of white blood cell that makes antibodies to fight infections.
Bone marrow: the soft part inside certain bones where new blood cells are made
Lymph nodes: Organs of the immune system, located throughout the body, that store lymphocytes and filter pathogens such as viruses and bacteria.
Spleen: An organ of the immune system, located in the abdomen, that stores and filters blood cells.

How do ibrutinib and chlorambucil work?

- Ibrutinib is a drug that works by blocking a protein called Bruton's tyrosine kinase, or BTK. Blocking BTK stops leukemia cells from growing and dividing. This is because leukemia cells need BTK to survive and grow.
- Chlorambucil is a chemotherapy drug that stops or slows the growth of cancer cells by damaging their **DNA**. When the DNA is damaged, the cancer cells cannot divide into new cells or repair themselves, and they die.

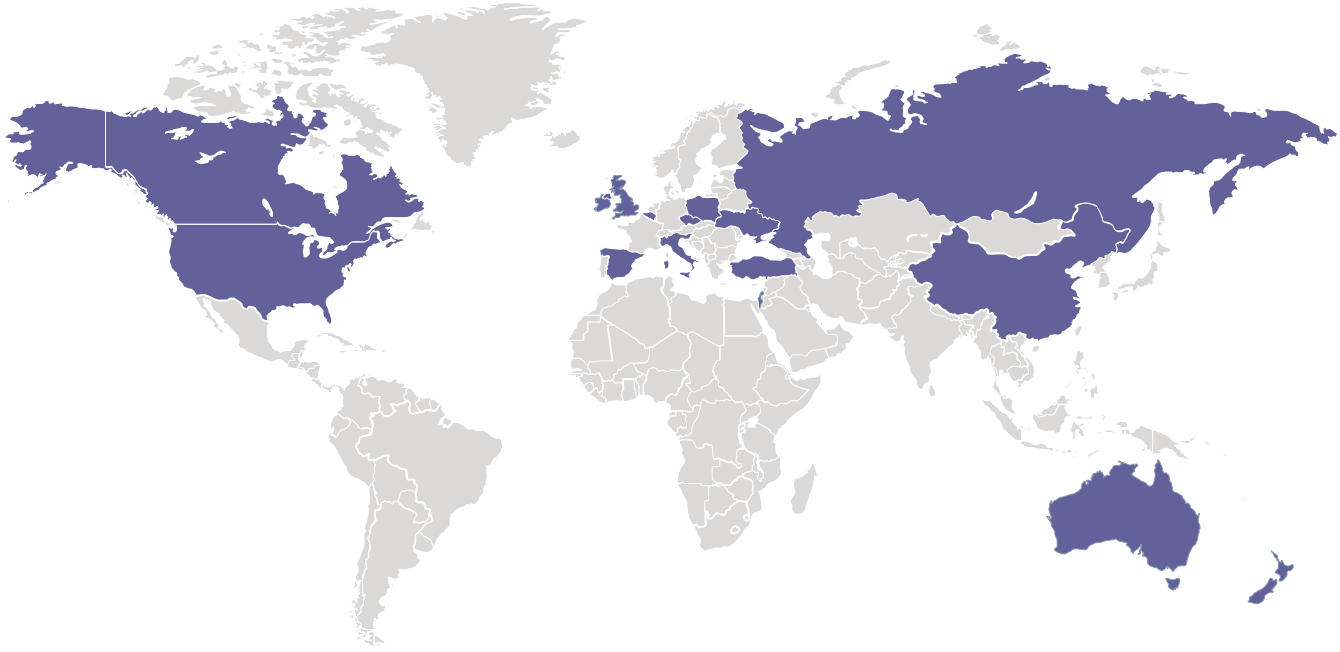
DNA: Genetic material that contains instructions for everything that a cell does.



Who took part in this study? Where were they from?

- A total of 269 adults with CLL/SLL participated in the RESONATE-2 study and met these conditions:
  - Were 65 years of age or older
  - Had a diagnosis of CLL or SLL needing treatment because of worsening blood counts, large spleen, large lymph nodes, or other symptoms caused by CLL/SLL (unexplained weight loss, **fatigue**, **fever**, or night sweats)
  - Had not received any previous treatment for CLL/SLL
- People could not take part in the study if they had deletion of chromosome 17p, a genetic change that makes the disease have a lower chance of responding to chemotherapy drugs like chlorambucil.
- Participants were enrolled at cancer centers in the United States, Canada, Europe, Russia, Turkey, Israel, China, Australia, and New Zealand.

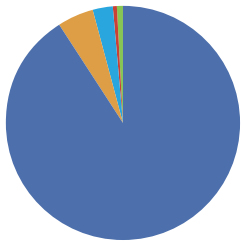
Fatigue: Getting tired more easily.
Fever: Higher than normal body temperature.



Of the 269 participants in the study:

63% (169 out of 269) were men

37% (100 out of 269) were women



91% (245 out of 269) were White

5% (13 out of 269) were Asian

3% (8 out of 269) were Black/African–American

<1% (1 out of 269) were Pacific Islanders

1% (2 out of 269) were of unknown race

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What happened to the participants in this study?

Researchers compared the results from the two groups to understand if taking ibrutinib helped people with CLL/SLL live longer without their disease getting worse compared to people taking chlorambucil.

Before starting treatment, some participants in the study had changes in specific **genes**, referred to as "high-risk" genetic changes, that make their disease grow more quickly or have a lower chance of responding to older types of treatment such as **chemotherapy**. These high-risk genetic changes include:

- Deletion of **chromosome** 11q, referred to as del(11q)
- Low genetic variation in the immunoglobulin heavy chain variability region (IGHV) gene, referred to as unmutated IGHV

Researchers looked at these high-risk participants to see how well ibrutinib worked.

Chemotherapy: Drugs that kill cancer cells by stopping them from dividing or damaging their DNA.
Chromosome: A long strand of DNA containing many genes.
Gene: A section of DNA that acts as instructions to make a functional molecule or protein.

March 2013

The RESONATE-2 study started in March 2013 and is ongoing
This report includes data collected until May 2021

May 2021

Participants were randomly split into two groups. One group took ibrutinib, and the other group took chlorambucil.

136 participants took ibrutinib

133 participants took chlorambucil

269 participants

Participants took

420 mg of ibrutinib once a day until worsening of disease or intolerable side effects

OR

Chlorambucil 0.5–0.8 mg/kg every 2 weeks for up to 48 weeks

Participants were followed for up to 8 years

What were the key questions answered in the RESONATE-2 study?

The RESONATE-2 study aimed to find out how well ibrutinib works, compared with chlorambucil, in people with CLL/SLL by answering the following questions:

How long do study participants live without worsening of their disease?

This was the main question of the study. To answer this question, the researchers looked at how long participants remained alive without worsening of their disease after starting study treatment. Disease is considered to be getting worse if a patient has one or more of the following: at least 50% increase in the size of lymph nodes or new large lymph nodes, at least 50% increase in the size of the liver and/or spleen or new large liver/spleen, at least 50% increase in the number of **lymphocytes** in the blood (unless this occurs at the same time that there is an improvement in other measurements), a decrease in **hemoglobin** and/or **platelets** due to CLL/SLL, or transformation to a more aggressive type of blood cancer.

Hemoglobin: The protein in red blood cells that carries oxygen.
Lymphocytes: A specialized type of white blood cell that helps to fight infections.
Neutrophil: a type of white blood cell that helps to heal injuries and fight infections
Platelet: A type of blood cell that helps to form blood clots to stop or prevent bleeding.

How many study participants respond to treatment?

To answer this question, the researchers looked at the number of participants who had improvement in their disease, called a response.

A participant is considered to have a "complete" response if the size of the lymph nodes, liver, and spleen have returned to a normal size seen in healthy people, the number of lymphocytes and other blood cells are in the range seen in healthy people, and the participant has no disease-related symptoms.

A participant is considered to have a "partial" response if they have at least 50% decrease in the size of large lymph nodes, at least 50% decrease in the size of the liver and/or spleen size, and at least 50% improvement in hemoglobin, **neutrophils**, or platelets (if these were abnormal before starting treatment).

How long do study participants live overall?

To answer this question, the researchers looked at how long participants remained alive after starting study treatment.

What are the side effects of treatment?

To answer this question, researchers looked at any side effects (undesirable effects) that participants had during the study. These side effects could have been caused by the study treatment, by the cancer itself, or by other illnesses or medications.

Because participants who took chlorambucil completed their treatment within 48 weeks, long-term side effects were only monitored for participants who took ibrutinib.

What other medications were participants in this study taking?

Because people who are 65 years of age or older are often taking medications to treat illnesses other than their cancer, the researchers also looked at what other medications participants were taking.

What did the researchers find?

Because participants in a clinical trial begin treatment at different times, not every participant had results at 8 years. Results are reported at 7 years because most participants had completed 7 years of follow-up.

How long did study participants live without worsening of their disease?

Alive without worsening of disease at 7 years

59% of participants treated with ibrutinib

9% of participants treated with chlorambucil

At 7 years after starting treatment, participants who took ibrutinib were more likely to be alive without worsening of disease than participants who took chlorambucil.

Alive without worsening of disease at 7 years
People with del(11q)

52% of participants treated with ibrutinib

0% of participants treated with chlorambucil

People with unmutated IGHV

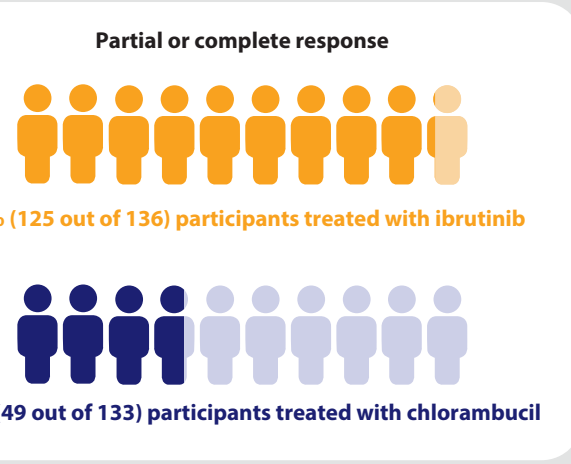
58% of participants treated with ibrutinib

2% of participants treated with chlorambucil

At 7 years after starting treatment, participants with high-risk genetic changes who took ibrutinib were more likely to be alive without worsening of disease than participants with high-risk genetic changes who took chlorambucil.

How many participants respond to treatment?

Participants who took ibrutinib were more likely to have a partial or complete response than participants taking chlorambucil.

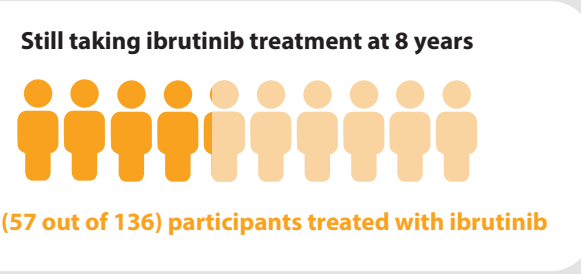


In participants taking ibrutinib, one-third of participants had complete response during the course of 7 years of follow-up after starting treatment.

How long do participants live overall?

Most of the participants who took ibrutinib were alive at 7 years after starting treatment.

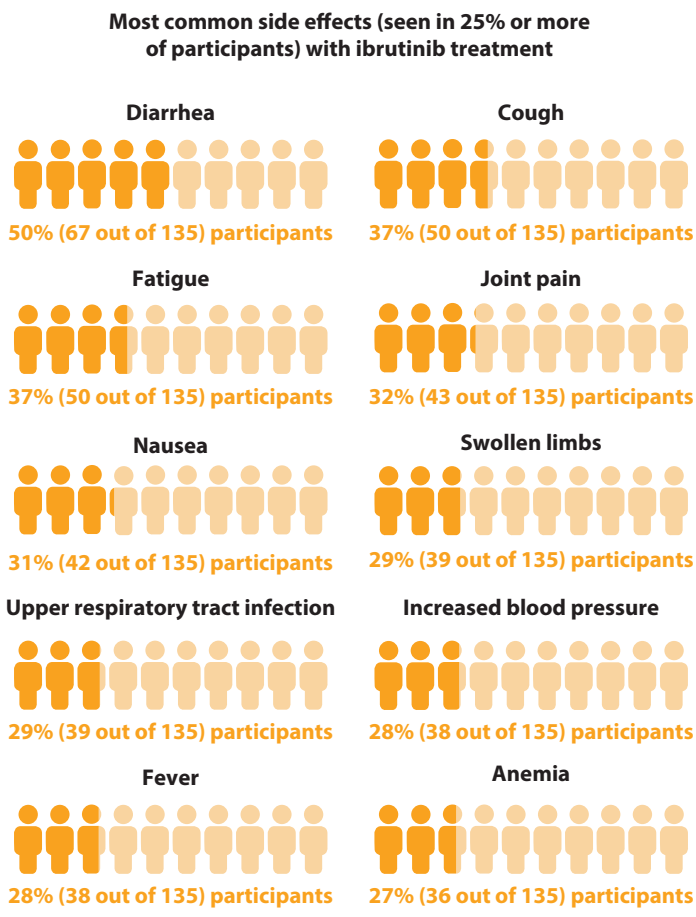
After up to 8 years, almost half of the participants were still taking ibrutinib treatment.



What are the side effects of treatment?

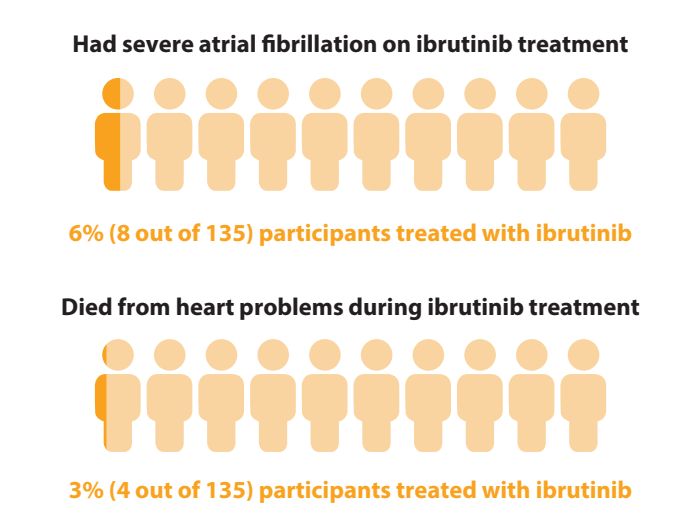
Side effects were most common in the first year after starting treatment with ibrutinib. Most side effects decreased over time in participants who kept taking ibrutinib.

Some participants experienced side effects that needed care by a doctor. Doctors could help prevent or lessen side effects by giving other medications, holding back one or more doses of ibrutinib, or lowering the dose of ibrutinib.

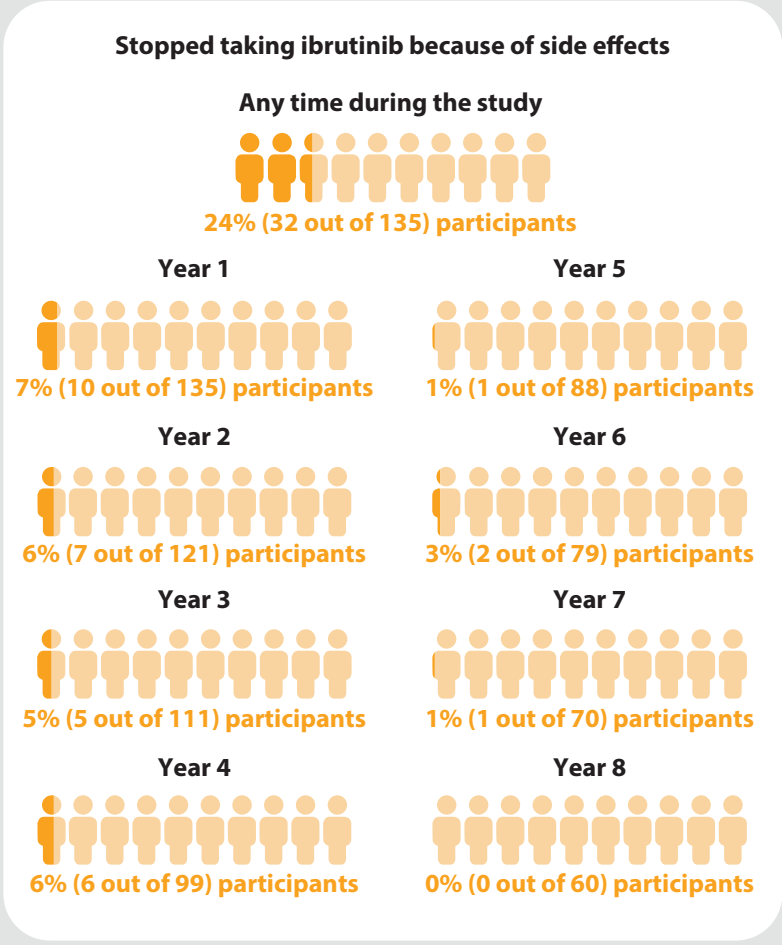


Heart problems such as atrial fibrillation, a condition which causes and irregular and often very fast heart rate, are rare side effects of ibrutinib treatment.

- Some participants had severe atrial fibrillation (atrial fibrillation with symptoms needing a procedure or surgery to restore a normal heart rhythm) during ibrutinib treatment.
- A small number of participants died from heart problems during ibrutinib treatment.



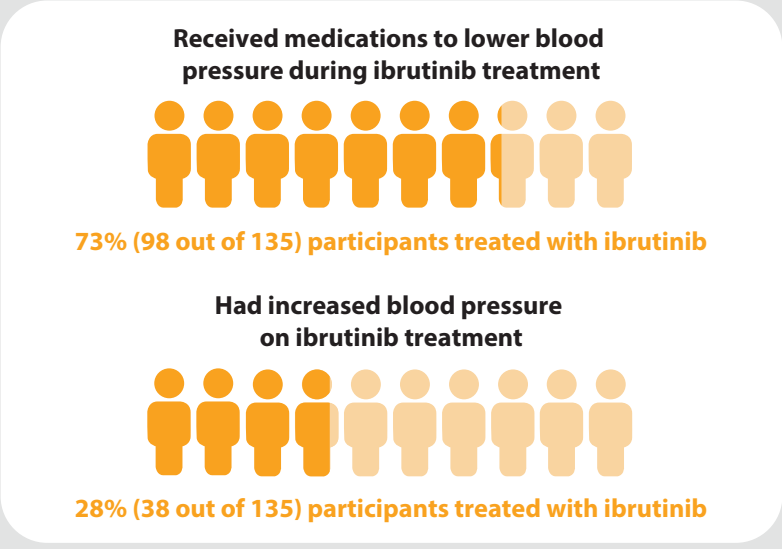
Some participants stopped taking ibrutinib because of side effects. Participants were most likely to stop treatment because of side effects in the first few years after starting treatment.



What other medications were participants in this study taking?

Older adults like those included in this study are very often taking medications to lower their blood pressure. Increased blood pressure is a known side effect of ibrutinib treatment.

- Although most of the participants treated with ibrutinib were also taking medications to lower blood pressure, ibrutinib caused increased blood pressure in many participants.



Medications that prevent **blood clots** increase the risk of bleeding. Bleeding is also a known side effect of ibrutinib treatment, so taking these medications together might further increase the risk of bleeding.

- Although most of the participants treated with ibrutinib were also taking medications to prevent blood clots, few of these participants had severe bleeding (bleeding that requires **transfusion**, hospitalization, or is life threatening) during ibrutinib treatment.

Blood clot: A sticky clump of blood cells.
Transfusion: Transfer of blood or blood components from one person (the donor) into the bloodstream of another person (the recipient).

Medications that decrease stomach acid might affect how well certain oral medications (medications taken by mouth) work by reducing the amount of medication that is absorbed.

- Although many of the participants treated with ibrutinib were also taking medications to reduce stomach acid, this did not affect how likely these participants were to be alive without their disease getting worse at 7 years.

Received medications to prevent blood clots during ibrutinib treatment

73% (99 out of 135) participants treated with ibrutinib

Had severe bleeding on ibrutinib treatment

8% (11 out of 135) participants treated with ibrutinib

Received medications to decrease stomach acid during ibrutinib treatment

64% (87 out of 135) participants treated with ibrutinib

Alive without worsening of disease at 7 years

61% of participants who received medications to decrease stomach acid

What do the results of this study mean?

- More study participants who were taking ibrutinib were alive without worsening of their disease at 7 years after starting treatment compared with participants who took chlorambucil.
- Most participants who were taking ibrutinib were alive at 7 years after starting treatment.
- Side effects decreased over time in participants who were taking ibrutinib, showing that it continues to be safe as a long-term treatment.
- Side effects observed in this study confirm what has been seen in earlier studies.
- Some participants had their dose of ibrutinib lowered because of side effects. Most of these participants were able to stay on treatment and continue to benefit from ibrutinib.
- Although most of the older adults in this study were also receiving medications for other illnesses, almost half of the participants (42%) were able to stay on ibrutinib treatment for up to 8 years.

Who sponsored the study? Who prepared this summary?

- This study was sponsored by Pharmacyclics LLC, an AbbVie Company.
- This summary was prepared by Melanie Sweetlove, MSc, of ApotheCom, and was funded by Pharmacyclics LLC, an AbbVie Company.
- The original authors of the presentation were involved in the preparation of this summary.

Further information

- The full name of the RESONATE-2 study is: Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Versus Chlorambucil in Patients 65 Years or Older With Treatment-Naive Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma.
- You can read more about the RESONATE-2 study on the following website: https://clinicaltrials.gov/ct2/show/NCT01722487

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Financial & competing interests disclosure

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