

## Summary of Clinical Trial Results

**A study comparing venetoclax with bendamustine (both with rituximab) in people with a type of slow-growing blood and bone marrow cancer called ‘chronic lymphocytic leukemia’ or ‘CLL’ that has returned or stopped responding to medicine or prior treatment**

See the end of the summary for the full title of the study.

### About this summary

This is a summary of the results of a clinical trial (called a ‘study’ in this document) – written for:

- members of the public and
- people who took part in the study.

This summary is based on information known at the time of writing.

The study started in March 2014 and finished in August 2022. This summary was written after the study had ended.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine.

This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your medicine.

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### Glossary

- CLL = chronic lymphocytic leukemia
- Refractory = when the cancer stops responding to medicine
- Relapse = when the cancer comes back even after it has been treated
- Bone marrow = spongy tissue found in the center of most bones

## Thank you to the people who took part in this study

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The people who took part have helped researchers to answer important questions about chronic lymphocytic leukemia and the medicines studied – ‘venetoclax combined with rituximab’ and ‘bendamustine combined with rituximab’.

### Key information about this study

#### Why was this study done?

- This study was done to look at two combinations of medicine in people with a type of blood and bone marrow cancer called ‘chronic lymphocytic leukemia’ – and to see how safe the medicines were.

#### Which medicines were studied and who took part?

- In this study, people were given a medicine called ‘venetoclax’ together with a medicine called ‘rituximab’ or a medicine called ‘bendamustine’ together with ‘rituximab’. It was decided by chance which medicine combination each person was given.
- This study included 389 people in 20 countries.

#### What were the results?

- The main finding was that it took longer for the cancer to get worse for people taking venetoclax with rituximab than for people taking bendamustine with rituximab.
- In 52% of the people (101 out of 194 people) taking venetoclax with rituximab there was at least one serious side effect, compared with around 45% of people (84 out of 188 people) taking bendamustine with rituximab.

## 1. General information about this study

### Why was this study done?

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A type of cancer that affects the blood and bone marrow, called 'chronic lymphocytic leukemia' or 'CLL', is still not curable even with better medicines over the years. Rituximab with bendamustine is a standard medicine for CLL. CLL often comes back after treatment with medicine (also known as relapse) and the cancer can also stop responding to medicine (also known as refractory). This means we need new medicines that work differently to help people whose CLL has relapsed or is refractory.

### What were the study medicines?

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This study looked at 2 medicines:

- Venetoclax together with rituximab (the new treatment combination)
- Bendamustine together with rituximab

#### **Venetoclax**

- You say this as 'ven – et – oh – klaks'.
- A protein (called 'B-cell lymphoma-2' or 'BCL-2') helps protect cancer cells from being killed by the body.
- Venetoclax works by joining with BCL-2, allowing the person's body to kill the cancer cells.

#### **Rituximab**

- You say this as 'ruh – tuhx – suh – mab'.
- This is a type of medicine that helps the immune system to recognize proteins on cancer cells.
- Rituximab may help other medicines that kill cancer cells to work better.

#### **Bendamustine**

- You say this as 'ben – da – muss – teen'.
- This is a medicine that kills cancer cells – called 'chemotherapy' or 'chemo'.
- This means that the cancer cells can't divide into new cells, so the cancer can't grow.

### What did researchers want to find out?

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- Researchers did this study to compare venetoclax and rituximab with bendamustine and rituximab – to see how well venetoclax with rituximab worked (see section 4 "What were the results of the study?").
- They also wanted to find out how safe the medicines were – by checking how many people had side effects and seeing how serious the side effects were, when taking each of the medicine combinations during this study (see section 5 "What were the side effects?").

#### **The main question that researchers wanted to answer was:**

1. How many people's cancer got worse, and how much time was there between the start of the study and people's cancer getting worse?

#### **Other questions that researchers wanted to answer included:**

2. How many people started a new anti-CLL medicine?
3. How many people died?

## What kind of study was this?

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This study was a ‘Phase 3’ study. This means that venetoclax had been tested in a smaller number of people with CLL before this study. In this study, a larger number of people with CLL either took venetoclax with rituximab or bendamustine with rituximab – this was to find out about the side effects of venetoclax with rituximab and if venetoclax with rituximab worked to change the amount of cancer in the body or helped people with CLL recover from cancer during the study. It can then be decided whether the medicine combination can be approved for doctors to give to patients.

The study was ‘randomized’. This means that it was decided by chance which of the medicines people in the study would have – like tossing a coin. Randomly choosing which medicine people take makes it more likely that the types of people in both groups (for example, age, race) will be a similar mix. Apart from the exact medicines being tested in each group, the way people were cared for was the same between the groups.

This was an ‘open label’ study. This means that both the people taking part in the study and the study doctors knew which of the study medicines people were taking.

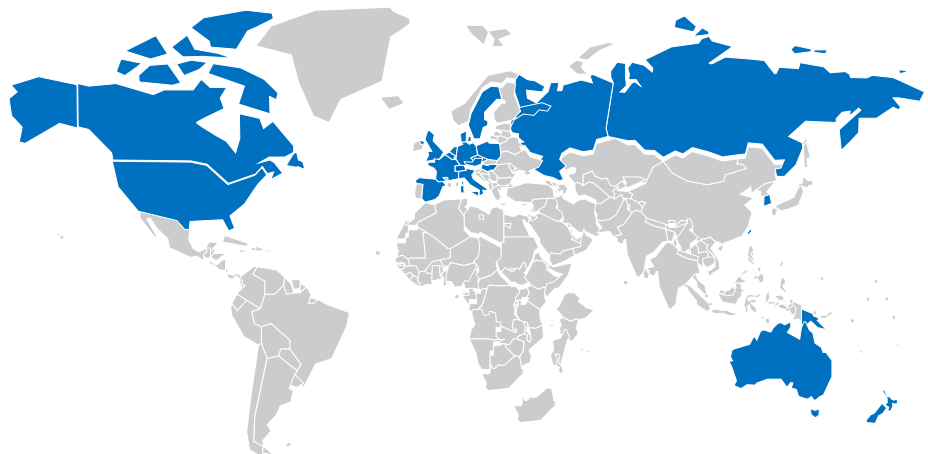
## When and where did the study take place?

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The study started in March 2014 and finished in August 2022. This summary was written after the study had ended.

The study took place at 111 centers – across 20 countries in North America, Oceania, Europe and Asia. The following map shows the countries where this study took place.

- Australia
- Austria
- Belgium
- Canada
- Czechia
- Denmark
- France
- Germany
- Hungary
- Italy
- New Zealand
- Poland
- Republic of Korea
- Russian Federation
- Spain
- Sweden
- Taiwan
- The Netherlands
- United Kingdom
- United States



## 2. Who took part in this study?

In this study, 389 people with CLL took part.

People who took part in the study were 18 years of age or older. 287 of the 389 people (74%) were male and 102 of the 389 people (26%) were female.

People could take part in the study if:

- They had CLL that had returned or stopped responding to medicine.
- They had previously been treated for CLL 1 to 3 times, including chemotherapy at least once.
- They had an Eastern Cooperative Oncology Group (also known as ECOG) performance score of 1 or 0, which means that they were able to perform activities as well or almost as well as they could before they had the illness.
- Their kidney system and liver system were working well.

People could not take part in the study if:

- They had previously received healthy blood-forming cells from a donor – called an ‘allogenic stem cell transplant’.
- Their CLL had transformed to cancer of the lymph nodes – called ‘aggressive non-Hodgkin’s lymphoma’.
- They had another type of cancer in addition to CLL.
- They had been treated with venetoclax before or an anti-cancer medicine within 28 days before taking part in the study.

## 3. What happened during the study?

During the study, people were selected to get one of 2 medicines. The medicines were selected at random – by a computer.

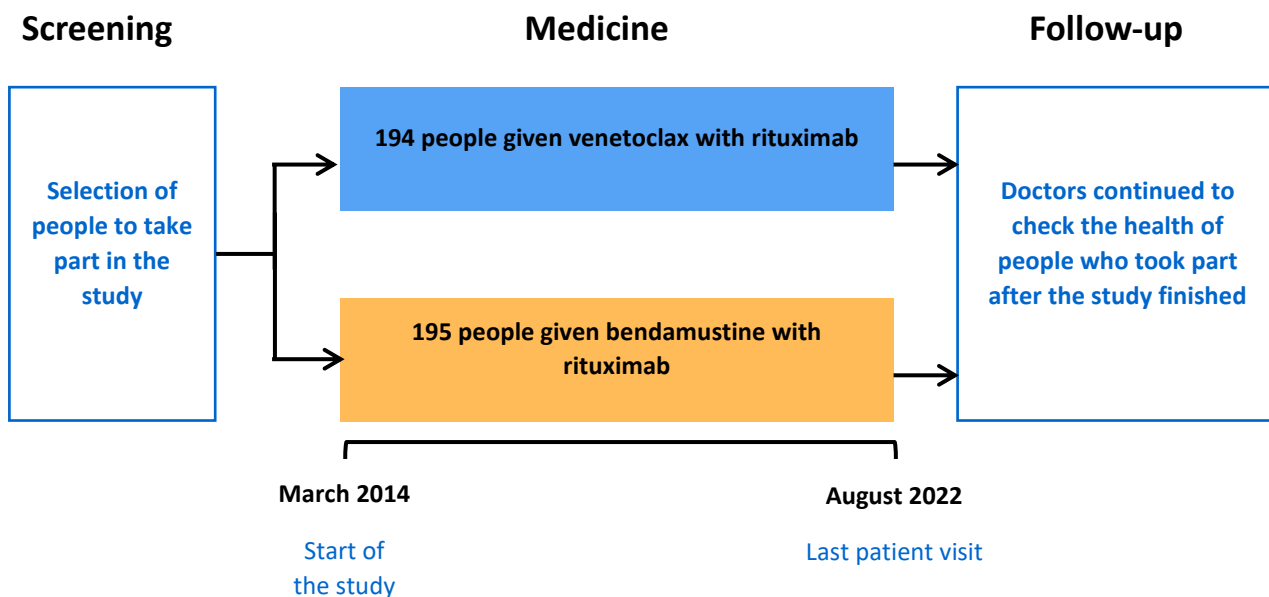
The medicines in this study were given in ‘treatment cycles’. For this study, each treatment cycle lasted for 28 days and there were 6 treatment cycles in total.

The medicine groups were:

- **Group A: venetoclax combined with rituximab** – venetoclax taken daily as tablets by mouth and a drip (infusion) of rituximab into a vein on day 1 of each treatment cycle.
- **Group B: bendamustine combined with rituximab** – a drip (infusion) of bendamustine into a vein on day 1 and 2 of each treatment cycle and a drip (infusion) of rituximab into a vein on day 1 of each treatment cycle.

People continued to receive medicine until they had too many side effects, their disease got worse, or they stopped the study for other defined reasons. At the end of the study, patients in both groups who needed medicine were allowed to be re-treated and take venetoclax with rituximab.

The study flowchart below has more information about what happened in the study.



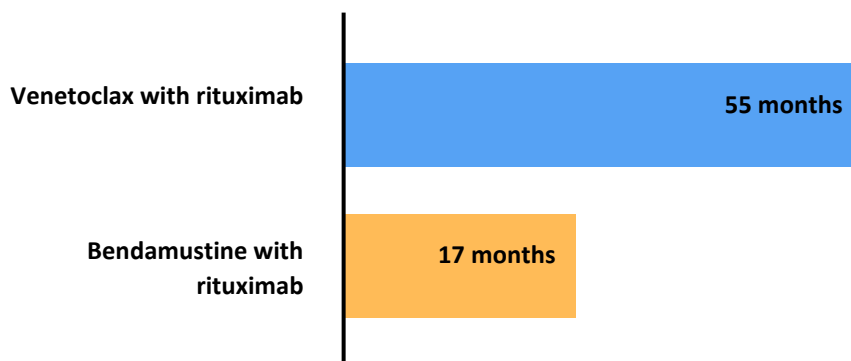
## 4. What were the results of the study?

**Question 1:** How many people’s cancer got worse, and how much time was there between the start of the study and people’s cancer getting worse?

Researchers looked at different characteristics that show people’s cancer has got worse.

- In the venetoclax with rituximab group, 136 out of 194 (70%) people’s cancer got worse. This happened around 55 months from the start of the study.
- In the bendamustine with rituximab group, 173 out of 195 (89%) people’s cancer got worse. This happened around 17 months from the start of the study.

### How long did it take until people’s cancer got worse?

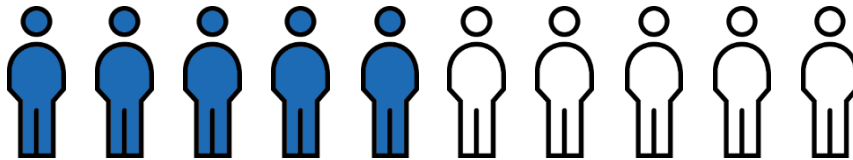


## Question 2: How many people started a new anti-CLL medicine?

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Another piece of information that researchers collected was how many people had to start a new anti-CLL medicine for their cancer and stop taking one of the medicine combinations in this study.

- In the venetoclax with rituximab group, around 49% of people started new medicine by the end of the study.
- In the bendamustine with rituximab group, around 67% of people started new medicine by the end of the study.



**Around 5 in every 10 people (49%) started new anti-CLL medicine in the venetoclax with rituximab group**



**Around 7 in every 10 people (67%) started new anti-CLL medicine in the bendamustine with rituximab group**

## Question 3: How many people died?

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Researchers also looked at how many people died during the study.

- In the venetoclax with rituximab group, 26 out of 194 (13%) people died.
- In the bendamustine with rituximab group, 28 out of 195 (14%) people died.

This section only shows the key results from this study. You can find information about all other results on the websites at the end of this summary (see section 8).

## 5. What were the side effects?

Side effects are medical problems (such as feeling dizzy) that happen during the study.

- They are described in this summary because the study doctor believes the side effects were related to the medicines in the study.
- Not all the people in this study had all of the side effects.
- Side effects may be mild to very serious and can be different from person to person.

It is important to be aware that the side effects reported here are from this single study. Therefore, the side effects shown here may be different from those seen in other studies, or those that appear on the medicine leaflets.

Serious and common side effects are listed in the following sections.

### Serious side effects

A side effect is considered 'serious' if it is life-threatening, needs hospital care, or causes lasting problems.

In the bendamustine with rituximab group, 7 people were excluded in the side effects reports due to not having a valid dose of the medicine. During this study, almost 5 in every 10 people (48%) had at least one serious side effect. Around 52% of people taking venetoclax with rituximab had a serious side effect, compared with around 45% of people taking bendamustine with rituximab.

The most common serious side effects are shown in the following table – these are the most common serious side effects across both medicine groups which occurred in 10% of people in either medicine group. Some people had more than one side effect – this means that they are included in more than one row in the table.

<b>Most serious side effects reported in this study</b>	<b>People taking venetoclax with rituximab (194 people total)</b>	<b>People taking bendamustine with rituximab (188 people total)</b>
Infections and infestations	21% (41 out of 194)	24% (45 out of 188)
Problems with blood and other body fluids such as 'lymph'	10% (19 out of 194)	15% (28 out of 188)
Uncontrolled growth of cells or tissues – noncancerous, cancerous and unspecified	11% (22 out of 194)	9% (16 out of 188)

There were some people in the study who died due to side effects that may have been related to one of the study medicines. These were:

- 18 out of 194 people (9%) in the venetoclax with rituximab group.
- 17 out of 188 people (9%) in the bendamustine with rituximab group.



During the study, some people decided to stop taking their medicine because of side effects:

- In the venetoclax with rituximab group, 37 out of 194 people (19%) stopped taking their medicine.
- In the bendamustine with rituximab group, 18 out of 188 people (10%) stopped taking their medicine.

### Most common side effects

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During this study, around 9 out of every 10 people (89%) had a side effect that was thought to be related to the study medicines. Around 88% of people taking venetoclax with rituximab had a side effect that was thought to be related to the study medicines, compared with around 90% of people taking bendamustine with rituximab.

The most common side effects are shown in the following table – these are the most common side effects across both medicine groups which occurred in at least 10% of people in either medicine group. Some people had more than one side effect – this means that they are included in more than one row in the table.

In the bendamustine with rituximab group, 7 people were excluded in the side effects reports due to not having a valid dose of the medicine.

Most common side effects reported in this study	People taking venetoclax with rituximab (194 people total)	People taking bendamustine with rituximab (188 people total)
Low level of white blood cells	23% (44 out of 194)	24% (45 out of 188)
Infusion-related reaction	9% (17 out of 194)	23% (43 out of 188)
Fever	2% (4 out of 194)	12% (22 out of 188)
Low level of the blood cell fragments that help blood to clot – called 'platelets'	1% (2 out of 194)	13% (24 out of 188)

### Other side effects

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You can find information about other side effects (not shown in the sections above) on the websites listed at the end of this summary – see section 8.

## 6. How has this study helped research?

The information presented here is from a single study of 389 people with CLL. These results helped researchers learn more about CLL that has returned or stopped responding to medicine, and how the combination of venetoclax with rituximab may be used to treat CLL.

In this study, it took longer for the cancer to get worse for those taking venetoclax with rituximab compared with those taking bendamustine with rituximab. Fewer people taking venetoclax with rituximab had to start new anti-CLL medicine than those taking bendamustine with rituximab. The side effects of venetoclax with rituximab were similar to those experienced by people taking the individual medicines in other studies.

No single study can tell us everything about the risks and benefits of a medicine. It takes lots of people in many studies to find out everything we need to know. The results from this study may be different from other studies with the same medicine.

- **This means that you should not make decisions based on this one summary – always speak to your doctor before making any decisions about your medicine.**

## 7. Are there plans for other studies?

At the time of writing this summary, no more studies looking at venetoclax with rituximab are planned.

## 8. Where can I find more information?

You can find more information about this study on the websites listed below:

- <https://clinicaltrials.gov/ct2/show/results/NCT02005471>
- <https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002110-12/results>

If you would like to find out more about the results of this study, the full title of the most recent relevant scientific paper is [“Enduring undetectable MRD and updated outcomes in relapsed/refractory CLL after fixed-duration venetoclax-rituximab”](#). The authors of the scientific paper are John F. Seymour, Thomas J. Kipps, Barbara F. Eichhorst, James D’Rozario, Carolyn J. Owen and others. The paper was published in 2022, in the journal ‘Blood’, volume number 140, on pages 839 to 850.

Additional scientific papers of this study include [Kater et al., \(2020\)](#), [Kater et al., \(2019\)](#), and [Seymour et al., \(2018\)](#).

## **Who can I contact if I have questions about this study?**

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If you have any further questions after reading this summary:

- Visit the ForPatients platform and fill out the contact form – <https://forpatients.roche.com/en/trials/cancer/leukemia/a-study-to-evaluate-the-benefit-of-venetoclax-plus-ritu-04186.html>
- Contact a representative at your local Roche office.

If you took part in this study and have any questions about the results:

- Speak with the study doctor or staff at the study hospital or clinic.

If you have questions about your own medicine:

- Speak to the doctor in charge of your medicine.

## **Who organized and paid for this study?**

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This study was organized and paid for by F. Hoffmann-La Roche Ltd who have their headquarters in Basel, Switzerland. Venetoclax is being developed by Genentech, Inc., a member of the Roche group, and AbbVie. It is jointly commercialized by Genentech, Inc. and AbbVie in the US, and commercialized by AbbVie outside of the US.

## **Full title of the study and other identifying information**

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The full title of this study is: [“A Study to Evaluate the Benefit of Venetoclax Plus Rituximab Compared With Bendamustine Plus Rituximab in Participants With Relapsed or Refractory Chronic Lymphocytic Leukemia \(CLL\) \(MURANO\)”](#).

The study is known as ‘MURANO’.

- The protocol number for this study is: GO28667.
- The ClinicalTrials.gov identifier for this study is: NCT02005471.
- The EudraCT number for this study is: 2013-002110-12.