Summary of Clinical Trial Results

VERONICA: A study looking at venetoclax and fulvestrant for patients with oestrogen receptor-positive, HER2-negative, advanced breast cancer, after CDK4/6 inhibitor therapy

See the end of this document for the full title of the study.

About this summary

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

- members of the public (including patients with breast cancer) and
- people who took part in the study.

This summary is based on information known at the time of writing. The study started in September 2018 and ended in May 2021. This summary mainly includes results up until August 2020, but also has some extra results from June 2021 (see section 6, "How has this study helped research?").

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 those of 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 treatment.**

Contents of the summary

Thank you to the people who took part in the study

The people who took part in the study have helped researchers to answer important questions about oestrogen receptor-positive, HER2-negative, advanced breast cancer and the medicines studied.

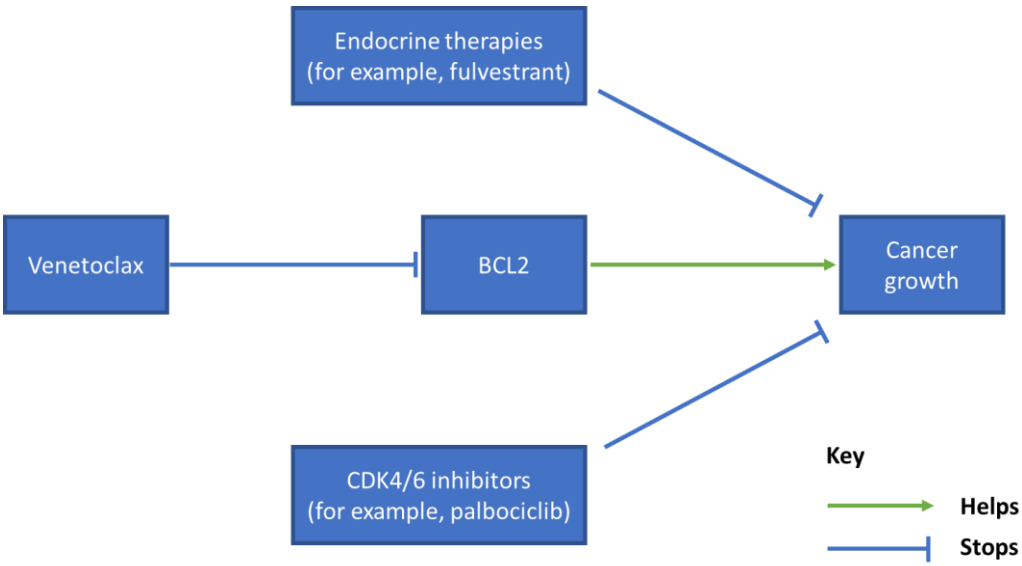
1. General information about the study

Why was this study done?

Hormone receptors are a type of protein found in some cancer cells. Breast cancers that have high levels of a type of hormone receptor, called the oestrogen receptor, are activated by the hormone oestrogen. This means that oestrogen in the body 'helps' the cancer to grow. Some breast cancers have high levels of oestrogen receptors, but low levels of another receptor, called HER2. This type of breast cancer is called oestrogen receptor-positive, HER2-negative breast cancer. In some patients, the cancer cells have spread to other parts of the body – this breast cancer is called 'advanced' (or 'metastatic' or 'stage four' cancer).

When first diagnosed with this type of cancer, patients are typically offered a combination of anti-cancer medicines. These include treatments that stop oestrogen from 'helping' the cancer cells to grow, which are called endocrine (hormone) therapies. An example is the medicine fulvestrant. Patients with oestrogen receptor-positive, HER2-negative, advanced breast cancer are also given treatments that target and block specific proteins called cyclin-dependent kinases (CDK) 4 and 6, which normally 'help' cancer cells to keep growing. These treatments are called CDK4/6 inhibitors, of which an example is the medicine palbociclib. However, in some patients, the cancer cells can still grow, so other medicines are needed to delay this.

Around 7 in every 10 patients with oestrogen receptor-positive, advanced breast cancer also have high levels of a protein called BCL2, which normally stops the cancer cell from dying and may be the cause of the continued cancer growth. This study was done to see how effective and safe a new treatment option that targets and blocks BCL2 (called venetoclax; see below) is when combined with fulvestrant. This study was carried out in women with oestrogen receptor-positive, HER2-negative, advanced breast cancer who have previously been given endocrine (hormone) therapy and CDK4/6 inhibitors.



What were the study medicines?

Oestrogen receptor-targeted therapies

Fulvestrant

- Pronounced 'full-*vest*-rant'
- Fulvestrant is an existing medicine that works by attaching to the oestrogen receptor on the surface of cancer cells, causing the cells to destroy the receptor. This stops the receptor sending signals that make the cancer cell grow.

BCL2-targeted therapies

Venetoclax

- Pronounced 'veh-*nee*-toe-clax'
- Venetoclax is the medicine being studied in VERONICA. It works by binding to the BCL2 protein and stopping it from working. This may 'help' to kill the cancer cells.
- Since May 2021, venetoclax has been approved by the United States Food and Drug Administration and European Medicines Agency for the treatment of chronic lymphocytic leukaemia and acute myeloid leukaemia (two types of cancer affecting the blood).

What did researchers want to find out?

- Researchers did this study to find out how effective the study medicine (venetoclax) was when it was combined with an existing medicine (fulvestrant). They wanted to compare treatment with venetoclax and fulvestrant with treatment with the existing medicine (fulvestrant) alone (see section 4, "What are the results of the study at this point?").
- They also wanted to find out how safe the medicines were – by checking how many women had side effects, when taking either the combination of venetoclax and fulvestrant, or fulvestrant alone (see section 5, "What side effects have been seen so far in the study?").

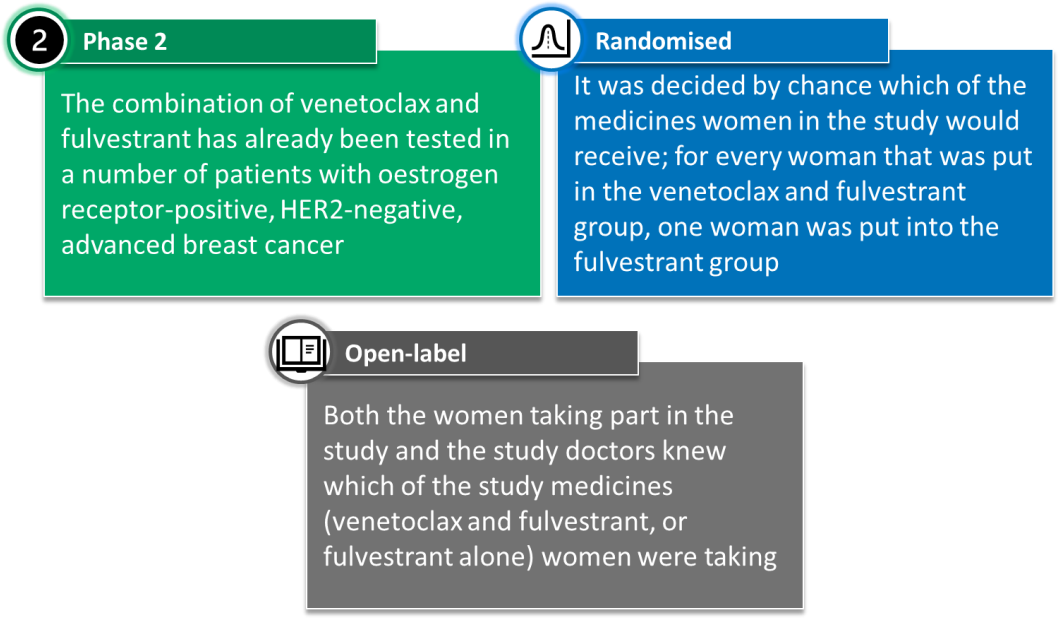
The main question that researchers wanted to answer was:

1. In how many women did treatment with the study medicine delay the woman's cancer from getting worse for at least 24 weeks (about 6 months)?

Other questions that researchers wanted to answer were:

2. How much time was there between the start of the study and women's cancer getting worse?
3. How many women had side effects, when taking either the combination of venetoclax and fulvestrant, or fulvestrant alone?

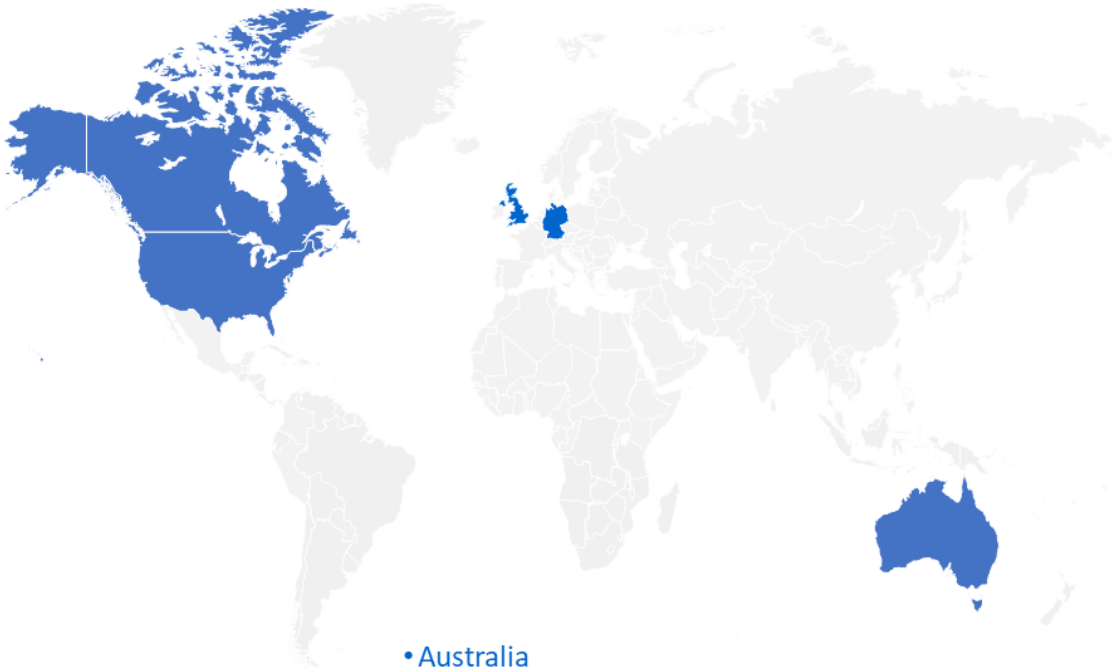
What kind of study was this?



When and where did the study take place?

The study started in September 2018 and finished in May 2021. This summary includes results up until August 2020, but also has some extra results from June 2021 (see section 6, “How has the study helped research?”).

The study took place at 40 study centres across 5 countries in Australia, North America and Europe. The following map shows the countries where this study took place.



- Australia
- Canada
- Germany
- United Kingdom
- United States

2. Who took part in the study?

In this study, 103 women with oestrogen receptor-positive, HER2-negative, advanced breast cancer took part. The majority of women (70%) were under 65 years old (age range: 32 to 86 years old).

Women could take part in the study if they:

- Had oestrogen receptor-positive, HER2-negative, advanced breast cancer (confirmed by testing)
- Were willing to provide samples of their tumour(s)
- Had previously been given endocrine (hormone) and CDK4/6 inhibitor therapies for advanced cancer (where the cancer cells have spread to other parts of the body), and their cancer had got worse

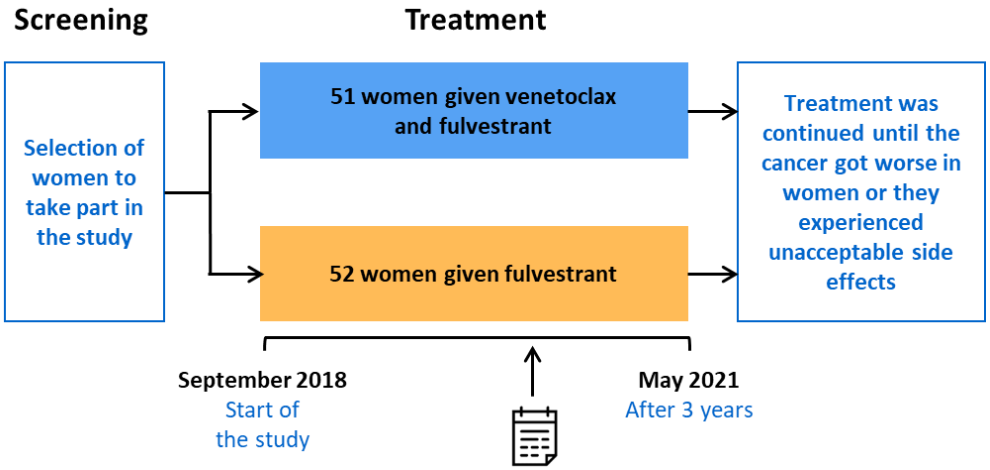
Women could NOT take part in the study if they:

- Had previously been given fulvestrant or venetoclax, or any other medicines that work in a similar way to fulvestrant or venetoclax
- Had any anti-cancer medicine in the 3 weeks before the study began
- Had cancer that had spread to the brain or spinal cord
- Had a type of cancer other than breast cancer in the past 5 years
- Had certain health problems, including a history of liver disease, inflammatory bowel disease or heart problems

3. What happened during the study?

During the study, women were selected by chance to get one of two treatments. The treatments were selected at random by a computer.
The treatment groups were:

- **Venetoclax** (the medicine being studied) and **fulvestrant** (the existing medicine) – venetoclax was taken orally as a tablet once a day; fulvestrant was injected into the woman's muscle once every 2 weeks for the first month, and then once a month after that.
- **Fulvestrant** (existing medicine) – fulvestrant was injected into the woman's muscle once every 2 weeks for the first month, and then once a month after that.

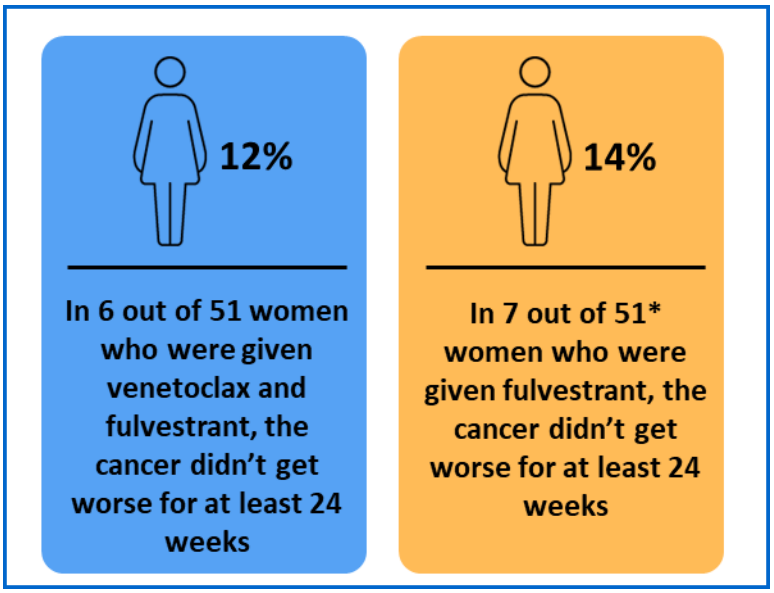


The symbol on the timeline (📋) shows where the information in this summary was collected – after 1 year and 11 months (August 2020). Some information up until June 2021 is also presented (see section 6, "How has the study helped research?").

4. What are the results of the study at this point?

Question 1: In how many women did treatment with the study medicine delay the woman's cancer from getting worse for at least 24 weeks (about 6 months)?

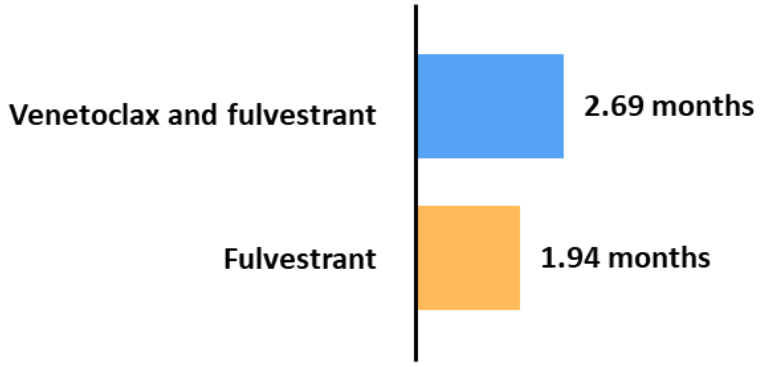
Researchers looked at whether, for at least 24 weeks (about 6 months), treatment with the study medicine delayed the woman's cancer from getting worse. The cancer didn't get worse for at least 24 weeks in nearly 12% of women who were given venetoclax and fulvestrant, compared with nearly 14% of women who were given fulvestrant.



*One woman had a cancer that could not be accurately measured at the start of the study and was excluded.

Question 2: How much time was there between the start of the study and women's cancer getting worse?

Researchers looked at the time between the start of the study and women's cancer getting worse. The median time (the middle time when all values are ordered by rank) was around 3 months in women who were given venetoclax and fulvestrant, compared with around 2 months for women who were given fulvestrant.



5. What side effects have been seen so far in the study?

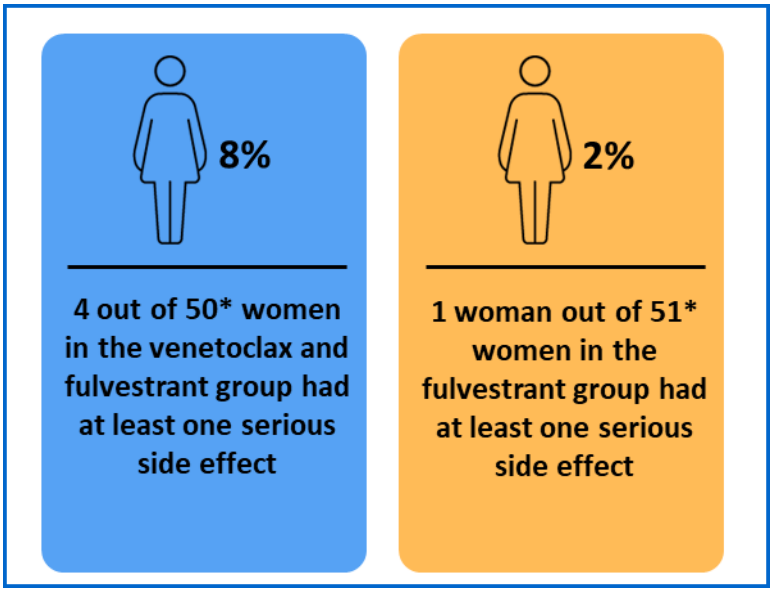
Side effects are unwanted medical problems (such as feeling dizzy) that happen during the study.

- Not all the women in this study had all of the side effects.
- Serious and common side effects are listed in the following sections.

Serious side effects

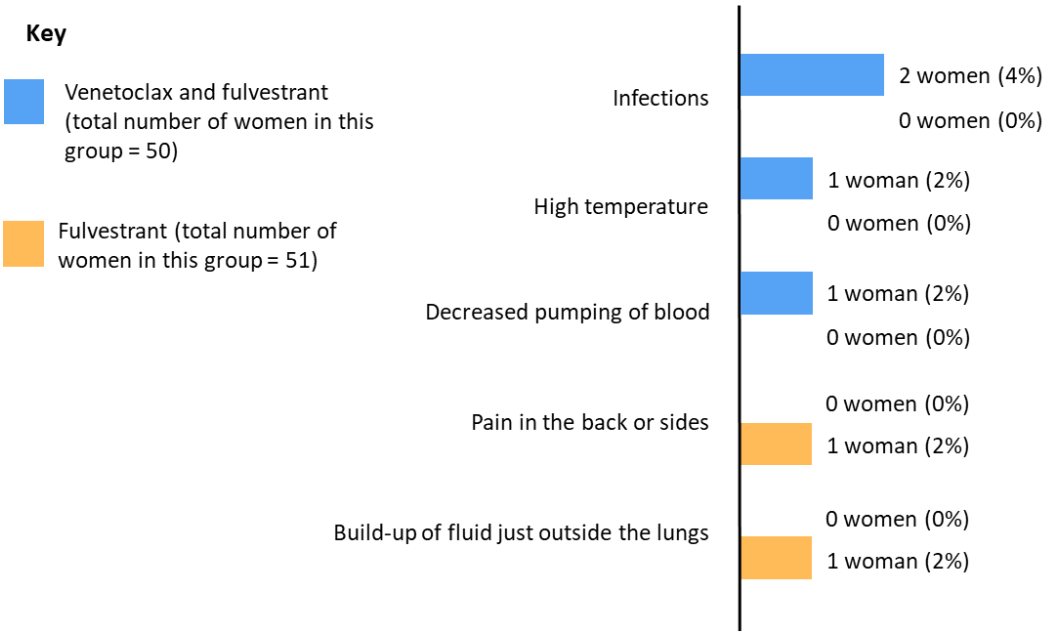
A side effect is considered 'serious' if it is life-threatening, needs hospital care or causes lasting problems.

During this study, 5 out of 101 women (5%) had at least one serious side effect.

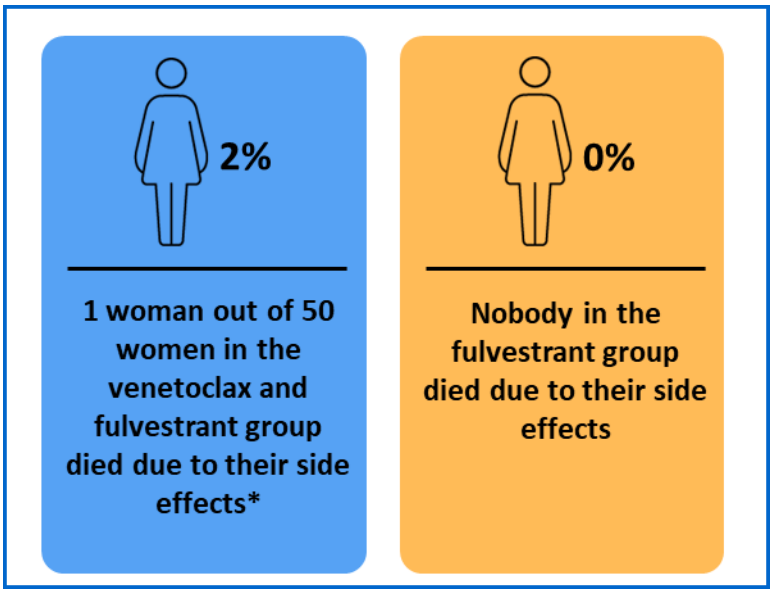


*One woman in each group did not receive the study medicine.

The most common serious side effects across both treatment groups are shown in the following bar chart:

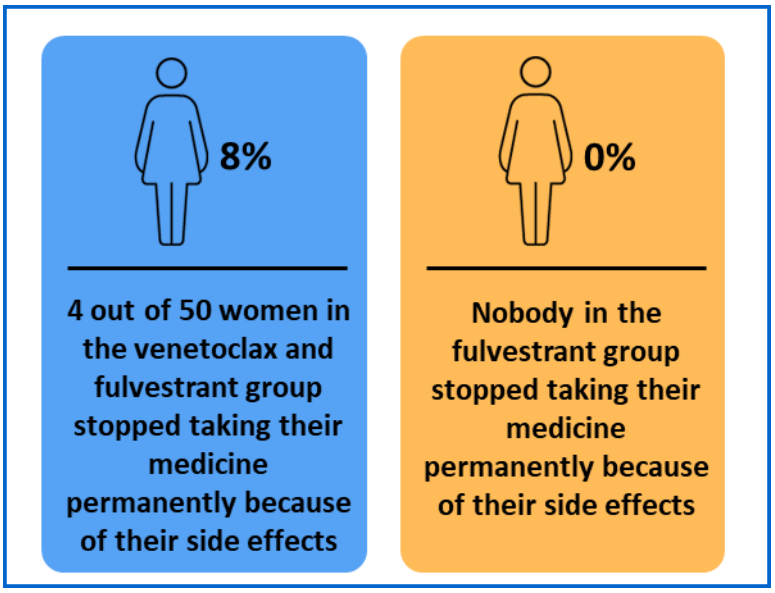


Overall, 19 women taking venetoclax and fulvestrant died during the study, compared with 9 women taking fulvestrant. Most of these deaths were due to women's cancer getting worse and happened more than a month after their last dose of study medicine.



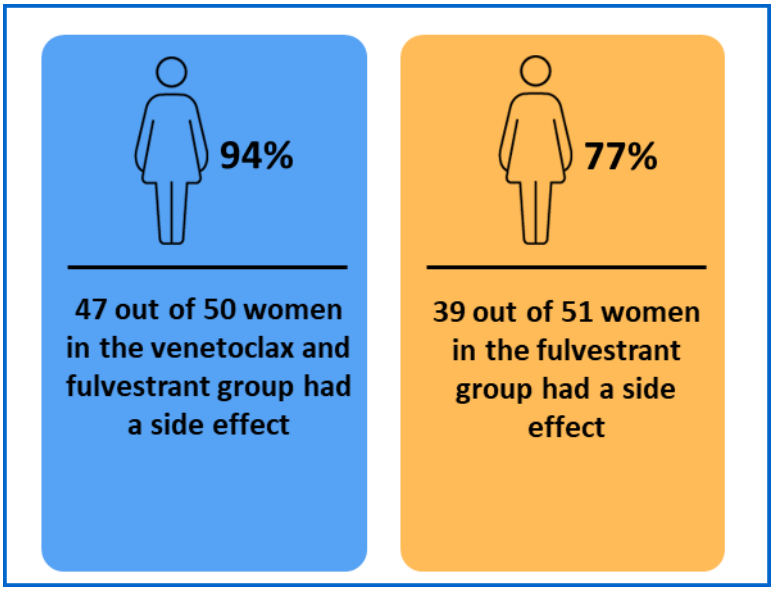
*This side effect, infection of the urinary tract, was not due to the study medicine, according to the study doctor who took care of the patient.

During the study, some women stopped taking their study medicine permanently because of their side effects.

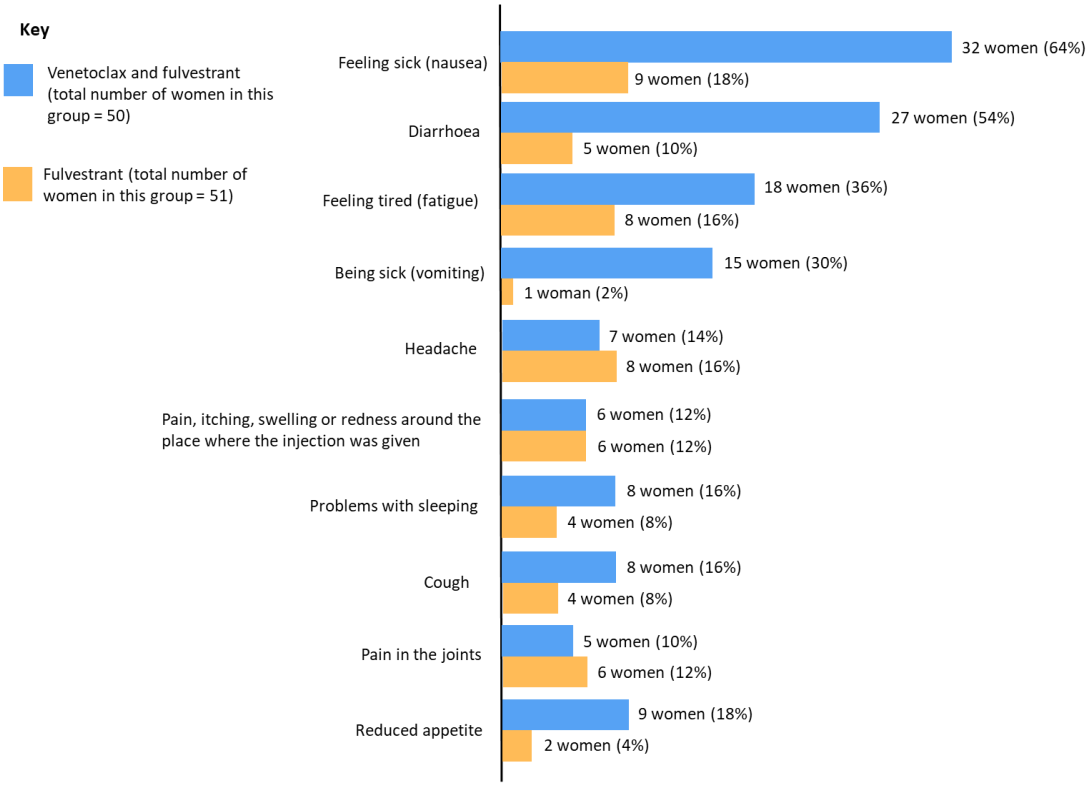


Most common side effects

During this study, across both treatment groups, most women (85%) had a side effect.



The 10 most common side effects across both treatment groups are shown in the following bar chart:



6. How has the study helped research?

The information presented here is from a single study of 103 women with oestrogen receptor-positive, HER2-negative, advanced breast cancer, who have previously been given endocrine (hormone) therapy and CDK4/6 inhibitors. This study has helped researchers understand whether combining venetoclax with fulvestrant helps to delay the cancer from getting worse in these women, compared with fulvestrant alone.

Treatment with venetoclax and fulvestrant did not help to delay the cancer from getting worse for at least 24 weeks (about 6 months), compared with fulvestrant alone, nor did it reduce the time between the start of the study and women's cancer getting worse.

Researchers also looked at whether adding venetoclax to fulvestrant helped women to live longer. As of June 2021, 48% (24 out of 58) of women given venetoclax and fulvestrant were still alive, compared with 65% (33 out of 51) of women given fulvestrant.

Overall, combining venetoclax and fulvestrant does not seem to be useful in patients with oestrogen receptor-positive, HER2-negative, advanced breast cancer who have previously been given endocrine (hormone) therapy and CDK4/6 inhibitors.

7. Are there plans for other studies?

At the time of writing this summary, no more studies looking at venetoclax in solid tumours are planned by F. Hoffmann-La Roche Ltd. As venetoclax is approved for some types of blood cancers, the drug will continue to be used for these as normal.

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/NCT03584009
- https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-005118-74/results
- https://forpatients.roche.com/en/trials/cancer/bc/a-phase-ii-study-comparing-the-efficacy-of-venetoclax---fulvestr.html

If you would like to find out more about the results of this study, the title of the relevant scientific paper is: "VERONICA: Randomized Phase II Study of Fulvestrant and Venetoclax in ER-Positive Metastatic Breast Cancer Post-CDK4/6 Inhibitors – Efficacy, Safety, and Biomarker Results". The authors of the publication are Geoffrey J. Lindeman, Tharu M. Fernando, Rebecca Bowen, Katarzyna J. Jerzak, Xinni Song, Thomas Decker, and others. The paper is published in 'Clinical Cancer Research', volume number 28, on pages 3256–3267.

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

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/bc/a-phase-ii-study-comparing-the-efficacy-of-venetoclax---fulvestr.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 treatment:

- Speak to the doctor in charge of your treatment.

Who organised and paid for this study?

This study was organised and paid for by F. Hoffmann-La Roche Ltd which has its headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: “A Phase II Study Comparing The Efficacy Of Venetoclax + Fulvestrant Vs. Fulvestrant In Women With Estrogen Receptor-Positive, Her2-Negative Locally Advanced Or Metastatic Breast Cancer Who Experienced Disease Recurrence Or Progression During Or After CDK4/6 Inhibitor Therapy (Veronica)”.

The study is known as ‘VERONICA’.

- The protocol number for this study is: WO40181.
- The ClinicalTrials.gov identifier for this study is: NCT03584009.
- The EudraCT number for this study is: 2017-005118-74.