A study to look at how effective and safe the drug combinations of obinutuzumab with polatuzumab vedotin and venetoclax, or rituximab with polatuzumab vedotin and venetoclax are in people with 'lymphoma' whose previous treatment had not worked or stopped working

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:

- a general audience, and
- people who took part in the study.

The study started in March 2016 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 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

Glossary

- NHL = a type of blood cancer of the lymph nodes called 'non-Hodgkin lymphoma'
- FL = follicular lymphoma (a type of NHL)
- DLBCL = diffuse large B-cell lymphoma (a type of NHL)
- G+Pola+Ven = obinutuzumab, polatuzumab vedotin and venetoclax
- R+Pola+Ven = rituximab, polatuzumab vedotin and venetoclax.

Thank you to the people who took part in this study

The people who took part in this study have helped researchers to answer important questions about two types of 'non-Hodgkin lymphoma' (NHL), called follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), and the medicines studied – 'obinutuzumab', 'rituximab', 'polatuzumab vedotin', and 'venetoclax'.

Key information about this study

- This study was done to find out how well two different combinations of medicines work, and how safe they are, in people with non-Hodgkin lymphoma (known as 'NHL'), whose previous treatment had not worked or had stopped working.
- In this study, people with follicular lymphoma (FL) were given obinutuzumab with polatuzumab vedotin and venetoclax (known as 'G+Pola+Ven'). People with diffuse large B-cell lymphoma (DLBCL) were given rituximab with polatuzumab vedotin and venetoclax (known as 'R+Pola+Ven'). These medicines were looked at in people with FL and DLBCL separately, because these diseases develop and behave differently.
- This study included 131 people in Italy, Australia and the United States (74 people with FL, and 57 people with DLBCL).
- In people with FL, the main finding was that 59% had no signs of cancer after completing treatment with G+Pola+Ven.
- In people with DLBCL, the main finding was that 31% had no signs of cancer after completing treatment with R+Pola+Ven.
- There were no new side effects for people who were given either of the new medicine combinations, compared with what we already know from when the individual medicines are given on their own
    - Overall, around 26% (19 out of 74) of people with FL taking G+Pola+Ven had serious side effects that were related to the study medicines
    - Around 12% (7 out of 57) of people with DLBCL taking R+Pola+Ven had serious side effects that were related to the study medicines.

1. General information about this study

Why was this study done?

Follicular lymphoma (known as 'FL') and diffuse large B-cell lymphoma (known as 'DLBCL') are types of non-Hodgkin lymphoma (known as 'NHL').

In follicular lymphoma:
B cells (also called B lymphocytes) are a type of white blood cell that help fight infections in the body. FL develops when B cells develop abnormally and build up to form a lump in pea-sized glands called lymph nodes, or in other body organs.

In diffuse large B-cell lymphoma:
DLBCL also develops when B cells grow abnormally, but it progresses faster and is more common than FL. It is called diffuse large B-cell lymphoma because when scientists look at the cells under a microscope, they are spread out ('diffuse') and large, instead of grouped together and small, like healthy cells. In the same way as FL, the abnormal cells build up in the lymph nodes or in other organs to form a lump.

Current treatments for follicular lymphoma and diffuse large B-cell lymphoma:
FL is currently treated with different combinations of medicines that kill cancer cells, including 'R-CHOP', 'BR' or 'R-CVP'. DLBCL is currently treated with R-CHOP. More than 6 out of every 10 people who have DLBCL will be cured after treatment with R-CHOP.[1] These medicine combinations are described below.

R-CHOP is a treatment made up of five different types of medicine**:**

- **R – rituximab** (this is a type of medicine called a 'monoclonal antibody', which is commonly used to treat cancer. Monoclonal antibodies are man-made proteins that stick to proteins (called 'antigens') on the surface of cancer cells, to help the immune system recognise the cancer and fight it)
- **C – cyclophosphamide** (a type of chemotherapy)
- **H – doxorubicin** (a type of chemotherapy)
- **O – vincristine** (a type of chemotherapy)
- **P – prednisone** (a steroid), **or other types of steroids.**

BR is a treatment made up of two different types of medicine**:**

- **B – bendamustine** (a type of chemotherapy)
- **R – rituximab** (a monoclonal antibody).

R-CVP is a treatment made up of four different types of medicine**:**

- **R – rituximab** (a monoclonal antibody)
- **C – cyclophosphamide** (a type of chemotherapy)
- **V – vincristine** (a type of chemotherapy)
- **P – prednisone** (a steroid), **or other types of steroids.**

Although these medicines usually work at first, in some people their FL or DLBCL may come back – this is called a 'relapse'. This means the medicine has stopped working. For other people with FL or DLBCL, these medicines may not work at all, and their disease may continue to get worse over time – this is called 'refractory' disease.

This study was done to find out if a new combination of medicines could be effective and safe for people with FL or DLBCL whose previous treatment had not worked at all or had stopped working.

What were the study medicines?

This study looked at 2 new combinations of medicines:

- **People with FL were given G+Pola+Ven:**
    - G = obinutuzumab
    - Pola = polatuzumab vedotin
    - Ven = venetoclax.

- **People with DLBCL were given R+Pola+Ven:**
    - R = rituximab
    - Pola = polatuzumab vedotin
    - Ven = venetoclax.

Obinutuzumab (you say this as 'oh-bi-nuh-TOO-zoo-mab') and **rituximab** (you say this as 'rih-TUK-si-mab'):
- These are a type of medicine called monoclonal antibodies
- These are proteins that are made in a laboratory
- They are designed to target specific proteins (called antigens) that are found on the surface of cancerous B cells
- This 'flags' the cancer cells and triggers the body's immune system to attack the cells and destroy them.

Polatuzumab vedotin (you say this as 'poh-la-TOO-zoo-mab veh-DOH-tin'):
- This is a type of medicine called an 'antibody–drug conjugate'
- It is made up of a combination of a monoclonal antibody that recognises cancer cells and attaches to them, and a 'chemotherapy' that enters these recognised cancer cells to kill them
- The effects of this medicine can stop the cancer from growing or spreading.

Venetoclax (you say this as 'veh-NEH-toh-klax'):
- This is a type of medicine called a 'BCL2 inhibitor'
- Some cancer cells make too much of a protein called BCL2, which keeps them alive and encourages them to grow
- This medicine blocks the BCL2 protein, helping to destroy cancer cells.

What did researchers want to find out?

The main questions that researchers wanted to answer were:

1. How many people with FL whose previous treatment(s) had not worked or had stopped working had their cancer shrink or disappear after taking G+Pola+Ven? (see section 4 'What were the results of this study?')
2. How many people with DLBCL whose previous treatment(s) had not worked or had stopped working had their cancer shrink or disappear after taking R+Pola+Ven? (see section 4 'What were the results of this study?')

Other questions that researchers wanted to answer included:

3. How safe was the combination of G+Pola+Ven for people with FL in this study? (see section 5 'What were the side effects?')
4. How safe was the combination of R+Pola+Ven for people with DLBCL in this study? (see section 5 'What were the side effects?')

What kind of study was this?

This was a 'Phase 1b/2' study. This means that all the medicines used in this study (obinutuzumab, rituximab, polatuzumab vedotin, and venetoclax) had been tested in a small number of people with FL or DLBCL before this study.

In this study, people with **FL** took **G+Pola+Ven**, and people with **DLBCL** took **R+Pola+Ven**. This was to find out if the two treatment combinations worked in treating their cancer, and if they were safe to use.

The study was an 'open-label' study, which means the participants and doctors both knew what treatments were being given.

The study was split into two parts:

- The first part was a **'dose-escalation'** phase. This is where people receive increasing doses of the medicine, to see how high the dose can get before the side effects get too strong. This phase shows scientists the best dose of the medicine to use – this is then called the 'recommended dose'
- The second part was a **'dose-expansion'** phase. This is where people receive the medicines at the recommended doses.

When and where did this study take place?

This study started in March 2016 and finished in August 2022. This summary was written after the study ended.

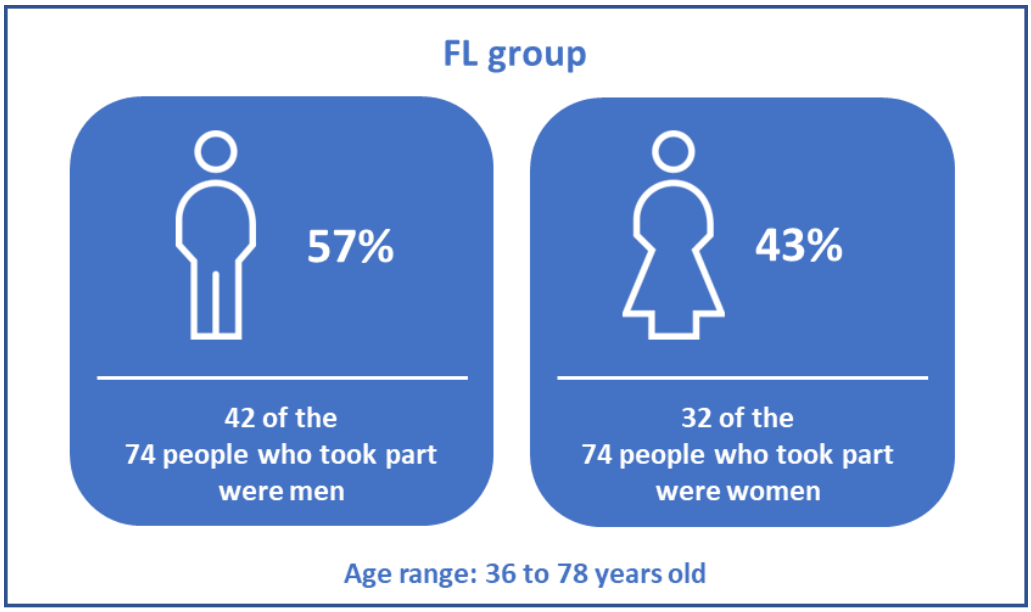
This study took place in 23 study sites across 3 countries – these were Italy (7 sites), Australia (6 sites) and the United States (10 sites).

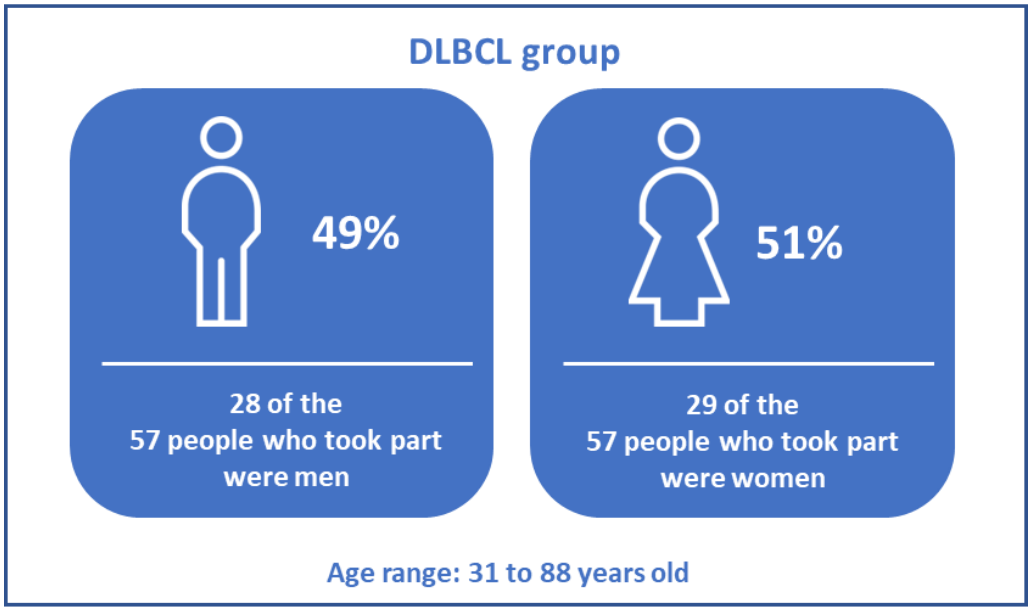
2. Who took part in this study?

In this study, 131 people with NHL took part – this included:

- 74 people with FL
- 57 people with DLBCL.

More information on the people who took part is given below:





People with FL or DLBCL could take part in the study if they:

- Were at least 18 years old
- Had 'CD20-positive' FL or DLBCL (CD20 is a marker, or antigen, on the surface of B cells that can be seen by scientists using a microscope)
- Had lymphoma, which is a type of blood cancer, that was visible on a positron emission tomography scan, also known as a 'PET scan' (this is a type of scan doctors use to see cancers)
- Had at least one lesion (this means a group of cancer cells) that doctors could measure with scans
- Had previously received at least one type of treatment that included chemotherapy and a monoclonal antibody (this is a type of medicine that helps the immune system to recognise and kill cancer cells) that targets cancer cells with the CD20 marker on them
- Had further cancer growth or spreading following previous treatment(s).

People could not take part in the study if they:

- Had Grade 3b FL (a severe form of FL)
- Previously had FL, which then further developed to become DLBCL
- Did not have the CD20 marker
- Had lymphoma that had spread to the central nervous system (this includes anywhere in the body's nerves, spine, or brain)
- Had received a type of treatment called stem cell transplant within 100 days of starting the study treatment. Stem cell transplants work by destroying unhealthy blood cells and replacing them with healthy blood cells that are taken from blood or bone marrow.

3. What happened during this study?

During the study people received one of the following treatment combinations:

- **G+Pola+Ven for people with FL**
- **R+Pola+Ven for people with DLBCL.**

In both the dose-escalation and dose-expansion phases, people were given 'induction' treatment with G+Pola+Ven (for people with FL) or R+Pola+Ven (for people with DLBCL). The treatments were given for 6 'cycles' – each treatment cycle lasted 21 days before starting again. For those whose induction treatment worked (the cancer shrunk or disappeared), people with FL were given 'maintenance' treatment with G+Ven for up to 2 years, and people with DLBCL were given 'consolidation' treatment with R+Ven for up to 8 months. 'Maintenance' treatment is a type of therapy continued for a long period of time to extend treatment response, whereas 'consolidation' treatment is continued for a shorter period of time to improve treatment response. Those whose induction treatment did not work did not receive either maintenance or consolidation therapy.

The **induction treatments** were:

- **G – obinutuzumab (for people with FL)** – injected into a vein once a week for the first 3 weeks of the first treatment cycle, then once every cycle for the other 5 treatment cycles
- **R – rituximab (for people with DLBCL)** – injected into a vein once in every cycle
- **Pola – polatuzumab vedotin** – injected into a vein once in every cycle
- **Ven – venetoclax** – taken as a tablet every day in every cycle.

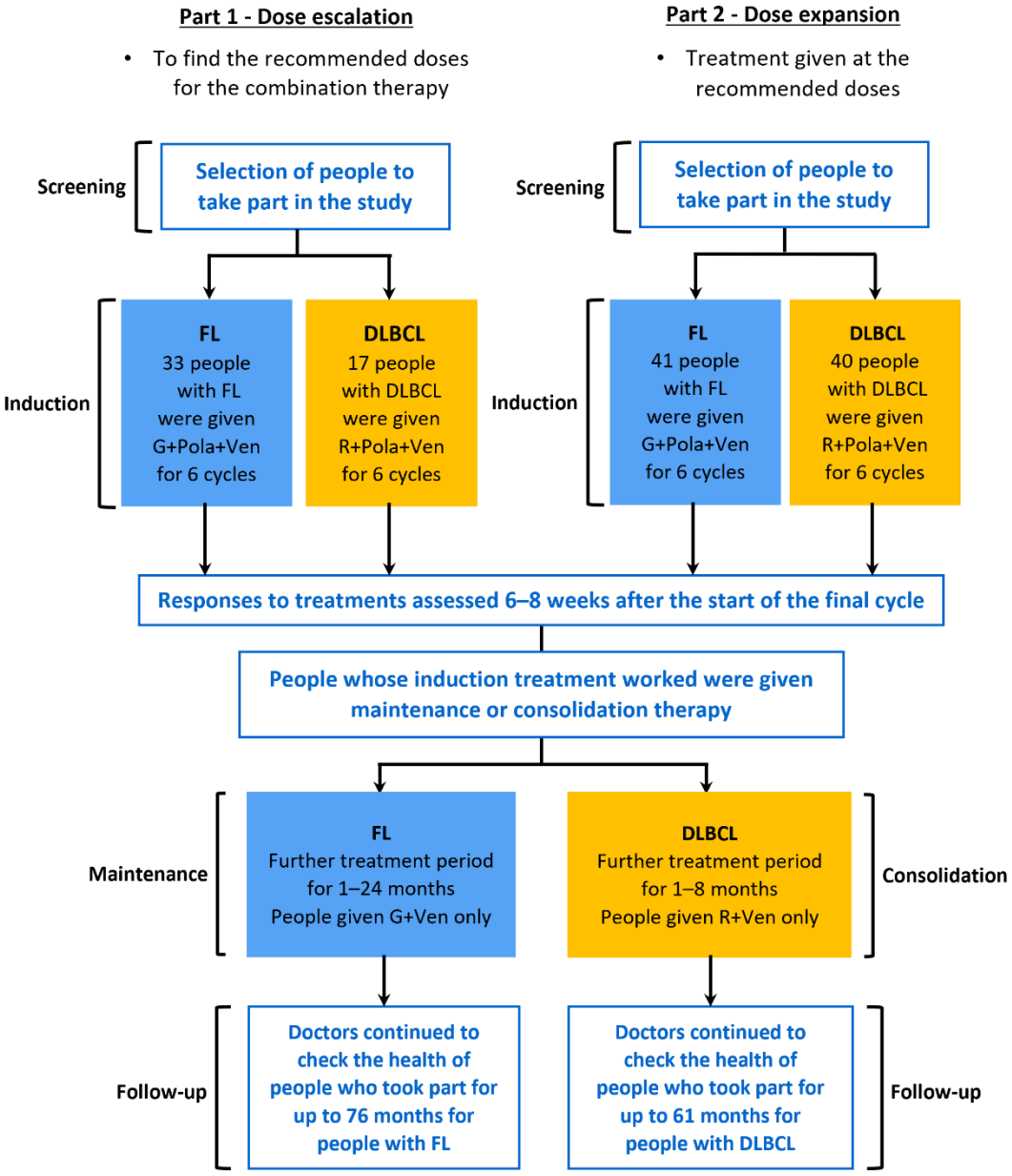
The **maintenance treatments** (for people with FL whose induction treatment worked) were:

- **G – obinutuzumab** – injected into a vein once every other month (starting in the second month) for up to 2 years
- **Ven – venetoclax** – taken as a tablet every day in every cycle for up to 8 months.

The **consolidation treatments** (for people with DLBCL whose induction treatment worked) were:

- **R – rituximab** – injected into a vein once every other month (starting in the second month) for up to 8 months
- **Ven – venetoclax** – taken as a tablet every day in every cycle for up to 8 months.

People in the study actually received the treatments for 0.2–29.3 months. Some patients took the treatments for a shorter time than others. This may be due to different reasons, such as experiencing side effects, or wishing to withdraw from the study. After their treatment had ended, the people who took part were asked to go back to their study centre for more visits – to check their overall health. Look below to see more information about what happened in the study.



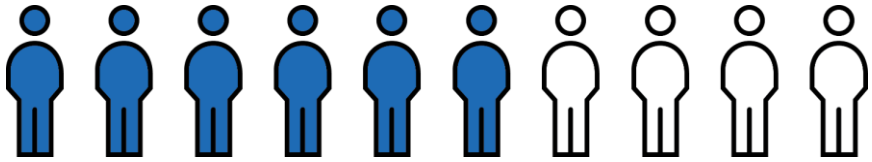
4. What were the results of this study?

The questions that researchers wanted to answer with this study are described below.

Question 1: How many people with FL whose previous treatment(s) had not worked or had stopped working had their cancer shrink or disappear after taking G+Pola+Ven?

Researchers looked at the proportion of people with FL who achieved a complete response after completing G+Pola+Ven induction treatment. A complete response means that the person no longer has any signs of FL.

Of the people with FL who were given G+Pola+Ven, 59% (29 people out of 49) had a complete response.

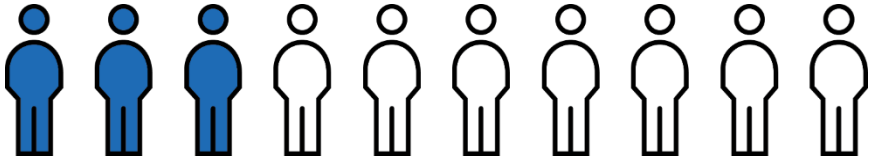


Almost 6 in every 10 people with FL (59%) had a complete response, which means they showed no signs of cancer after induction treatment.

Question 2: How many people with DLBCL whose previous treatment(s) had not worked or had stopped working had their cancer shrink or disappear after taking R+Pola+Ven?

The researchers also looked at the proportion of people with DLBCL who achieved a complete response after completing R+Pola+Ven induction treatment.

Of the people with DLBCL who were given R+Pola+Ven, 31% (15 people out of 48) had a complete response.



3 in every 10 people with DLBCL (31%) had a complete response, which means they showed no signs of cancer after induction treatment.

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 'Where can I find more information?').

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 treatments in the study
- Not all of 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.

Questions 3 and 4: How safe was the combination of G+Pola+Ven for people with FL and the combination of R+Pola+Ven for people with DLBCL in this study?

Serious side effects

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

Many of the common serious side effects in this study were related to how the person's immune system responded to the medicines. This is because several of the treatments given in this study work by targeting a type of white blood cell called 'B cells' that are an important part of the immune system. Although the treatments are effective at killing the cancerous B cells, a drop in the number of B cells in the body can also make people more prone to infections, which in some cases can be serious.

In people with FL receiving G+Pola+Ven, 19 out of 74 people (26%) had at least one serious side effect that was related to treatment.

In people with DLBCL receiving R+Pola+Ven, 7 out of 57 people (12%) had at least one serious side effect that was related to treatment.

The most common serious side effects are shown below. Some people had more than one side effect – this means that they are included more than once.

In people with FL receiving G+Pola+Ven:

- 4 out of 74 people (5.4%) had infusion-related reactions (reactions during the infusion of the medicines into the blood)
- 3 out of 74 people (4.1%) had pneumonia (an infection of one or both lungs)
- 3 out of 74 people (4.1%) had febrile neutropenia (abnormally high body temperature and low levels of a type of white blood cell called neutrophils)
- 2 out of 74 people (2.7%) had small intestinal obstruction (a blockage that keeps food or liquid from passing through your small intestine).

In people with DLBCL receiving R+Pola+Ven:

- 3 out of 57 people (5.3%) had neutropenia (low levels of neutrophils)
- 2 out of 57 people (3.5%) had diarrhoea (frequent bowel movements).

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:

- 2 out of 74 people (2.7%) with FL receiving G+Pola+Ven
- 1 out of 57 people (1.8%) with DLBCL receiving R+Pola+Ven.

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

- In the FL group receiving G+Pola+Ven:
    - 8 out of 74 people (11%) stopped taking obinutuzumab
    - 7 out of 74 people (9%) stopped taking polatuzumab vedotin
    - 12 out of 74 people (16%) stopped taking venetoclax.

- In the DLBCL group receiving R+Pola+Ven:
    - 6 out of 57 people (11%) stopped taking rituximab
    - 5 out of 57 people (9%) stopped taking polatuzumab vedotin
    - 7 out of 57 people (12%) stopped taking venetoclax.

Most common side effects

During this study, in people with FL receiving G+Pola+Ven, 71 out of 74 people (96%) had at least one side effect that was related to treatment and was not considered serious.

In people with DLBCL receiving R+Pola+Ven, 46 out of 57 people (81%) had at least one side effect that was related to treatment and was not considered serious.

The most common side effects are shown in the following table – these are side effects that occurred in at least 20% of people with FL receiving G+Pola+Ven or with DLBCL receiving R+Pola+Ven. Some people had more than one side effect – this means that they are included in more than one row in the table.

Most common side effects reported in this study	**People with FL taking G+Pola+Ven** (74 people total)
Diarrhoea (frequent bowel movements)	55% (41 out of 74)
Nausea (feeling sick)	47% (35 out of 74)
Neutropenia (low levels of a type of white blood cell called neutrophils)	43% (32 out of 74)
Fatigue (extreme tiredness)	38% (28 out of 74)
Infusion-related reactions (reactions during the infusion of the medicines into the blood)	34% (25 out of 74)
Cough (a reaction to an irritant in the throat or airways)	33% (24 out of 74)
Thrombocytopenia (low levels of a type of blood cell called platelets)	31% (23 out of 74)
Upper respiratory tract infection (infection of parts of the body involved in breathing, such as the sinuses, throat, airways or lungs)	31% (23 out of 74)
Vomiting (being sick)	28% (21 out of 74)
Peripheral neuropathy (nerve damage that can cause pain, numbness or weakness)	27% (20 out of 74)
Headache (continuous pain in the head or face)	23% (17 out of 74)
Constipation (infrequent bowel movements)	23% (17 out of 74)

Most common side effects reported in this study	People with DLBCL taking R+Pola+Ven (57 people total)
Neutropenia (low levels of a type of white blood cell called neutrophils)	53% (30 out of 57)
Diarrhoea (frequent bowel movements)	47% (27 out of 57)
Nausea (feeling sick)	37% (21 out of 57)
Vomiting (being sick)	30% (17 out of 57)
Fatigue (extreme tiredness)	26% (15 out of 57)
Pyrexia (an increase in body temperature/fever)	26% (15 out of 57)
Decreased appetite (reduced desire to eat)	25% (14 out of 57)
Anaemia (low levels of red blood cells or haemoglobin)	21% (12 out of 57)
Cough (a reaction to an irritant in the throat or airways)	21% (12 out of 57)

Other side effects

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 'Where can I find more information?'.

6. How has this study helped research?

The information presented here is from a single study of 131 people with FL or DLBCL – two types of blood cancer. These results helped researchers learn more about FL and DLBCL and the two new combinations of medicines – G+Pola+Ven and R+Pola+Ven.

The results presented in this summary are specifically relevant to people with FL or DLBCL that has come back after previous treatment (relapsed) or that did not respond to previous treatment (refractory).

All studies have limitations. An important limitation of this study is that it did not compare the new medicine combinations with the standard treatments that are usually given to people with relapsed or refractory FL or DLBCL. This means it is not as clear to scientists whether the new medicine combinations studied are better at treating cancer for people with relapsed or refractory FL or DLBCL than current standard treatments.

This study has shown that the new medicine combinations, G+Pola+Ven (for people with relapsed or refractory FL) and R+Pola+Ven (for people with relapsed or refractory DLBCL)

can help reduce cancer in patients. Also, people in this study did not have any new side effects aside from what we already knew when the individual medicines were given on their own.

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 of the same medicines.

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.

7. Are there plans for other studies?

At the time of writing this summary, no more studies looking at G+Pola+Ven for R/R FL, or R+Pola+Ven for R/R DLBCL 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/NCT02611323
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=GO29833
- https://forpatients.roche.com/en/trials/cancer/non-hodgkins-lymphoma/a-study-of-obinutuzumab--rituximab--polatuzumab-vedotin--and-ven.html

The full scientific paper for this study has not been published yet. However, if you would like to find out more about the results of this study, the full title of a relevant scientific abstract is: "Polatuzumab vedotin + obinutuzumab + venetoclax in patients with relapsed/refractory (R/R) follicular lymphoma (FL): Primary analysis of a phase 1b/2 trial.".

The authors of the scientific abstract are: Rajat Bannerji, Sam Yuen, Tycel Jovelle Phillips, Christopher Arthur, Iris Isufi, and others.

The abstract is published in the 'Journal of Clinical Oncology', volume number 39 (2021), on page 7534.

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/non-hodgkins-lymphoma/a-study-of-obinutuzumab--rituximab--polatuzumab-vedotin--and-ven.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 who have their headquarters in Basel, Switzerland.

Full title of the study and other identifying information

The full title of this study is: “A Phase Ib/II Study Evaluating the Safety and Efficacy of Obinutuzumab in Combination with Polatuzumab Vedotin and Venetoclax in Patients with Relapsed or Refractory Follicular Lymphoma and Rituximab in Combination with Polatuzumab Vedotin and Venetoclax in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma”.

- The protocol number for this study is: GO29833.
- The ClinicalTrials.gov identifier for this study is: NCT02611323.
- The EudraCT number for this study is: 2015-001998-40.

References

1. Sehn LH and Salles G. Diffuse Large B-Cell Lymphoma. The New England Journal of Medicine 2021;384:842–858.