Summary of Clinical Trial Results

A study to look at whether cobimetinib on its own and in combination with venetoclax, with or without atezolizumab, worked in people with a type of blood cancer called 'multiple myeloma' – and how safe this medicine was

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 November 2017 and finished in May 2021. 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 treatment.**

Contents of the summary

Glossary

- Bone marrow = spongy tissue found in the center of most bones
- Commercialized = a medicine that you can purchase over the counter or that your physician can order for you outside a clinical trial
- Randomization = the part of the study in which it was decided by chance which of the medicines people in the study would have
- Refractory = when the cancer stops responding to the treatment
- Relapse = when the cancer comes back even after it has been treated

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about multiple myeloma and the medicines studied – 'cobimetinib', 'cobimetinib together with venetoclax' and 'cobimetinib together with venetoclax and atezolizumab'.

Key information about this study

This study finished early, during the randomization phase, because the medicine combinations were not working well enough.

Why was this study done?

- This study was done to look at whether treatment with cobimetinib on its own or in combination with venetoclax, with or without atezolizumab, was safe in people with a type of blood cancer called 'multiple myeloma' – and whether these medicine combinations worked.

Which medicines were studied and who took part?

- In this study, people were given a medicine called cobimetinib, either on its own, together with a medicine called venetoclax, or together with venetoclax and a medicine called atezolizumab. It was decided by chance which treatment each person was given.
- Cobimetinib has been approved to treat a type of skin cancer called 'melanoma', but it is still being studied for the treatment of multiple myeloma.
- Venetoclax has been approved to treat other types of blood cancer called 'acute myeloid leukemia' and 'chronic lymphocytic leukemia', but it is still being studied in the treatment of multiple myeloma.
- Atezolizumab has been approved to treat lots of other types of cancer, but it is still being studied for the treatment of multiple myeloma.
- This study included 49 people in 8 countries.

What were the results?

- The study showed that:
  - Nearly everyone (94%) had a side effect that was thought to be related to their treatment.
  - Serious side effects that were thought to be related to the treatment were seen in under half (45%) of all people.
- The study also showed that some patients in every treatment group had a response to the treatment, except for the group given cobimetinib on its own.
  - In the safety phase, 17% of people in the group given cobimetinib with venetoclax had a response to the treatment, and 33% of people in the group given cobimetinib with venetoclax and atezolizumab had a response to the treatment.
  - In the randomization phase, no one (0%) in the group given cobimetinib had a response to treatment, 31% of people in the group given cobimetinib with venetoclax had a response to the treatment, and 27% of people in the group given cobimetinib with venetoclax and atezolizumab had a response to the treatment.

1. General information about this study

Why was this study done?

Multiple myeloma is a type of cancer that affects the bone marrow in various parts of the body. Multiple myeloma often comes back even after it has been treated (also known as a relapse) and the cancer can also stop responding to treatment (also known as refractory). Although new treatments have been able to help people with multiple myeloma live longer, these treatments cannot cure the cancer and the response to treatment does not last.

New treatments are needed to help people whose multiple myeloma is refractory or has relapsed.

What were the study medicines?

This study looked at 3 medicines:

- **Cobimetinib** on its own
- **Cobimetinib** together with **venetoclax**
- **Cobimetinib** together with **venetoclax** and **atezolizumab**

Cobimetinib

- You say this as 'coh – bee – met – in – ib'.
- This is a type of medicine that blocks signals that cancer cells use to divide and grow.
- Cobimetinib may help other medicines such as chemotherapy and immunotherapy to work better.

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 binding to BCL-2, allowing the person's body to kill the cancer cells.

Atezolizumab

- You say this as 'a – teh – zoh – liz – oo – mab'.
- This is a type of medicine known as 'immunotherapy'.
- Atezolizumab may be able to improve the immune system's ability to fight cancer.

What did researchers want to find out?

- Researchers did this study to find out how safe cobimetinib was, on its own and together with either venetoclax or venetoclax and atezolizumab – by checking how many people had side effects, and seeing how serious they were, when taking each of the medicine combinations during this study (see section 5 "What were the side effects?").
- They also wanted to see how well the medicine combinations worked (see section 4 "What were the results of the study?").

The main questions that researchers wanted to answer were:

1. How many people had side effects (that were thought to be linked to their treatment) during the study?
2. Was there a change in the amount of cancer present, and did the cancer get better or worse during the study?

Other questions that researchers wanted to answer included:

3. How much time was there between the start of the study and people's cancer getting worse?
4. For people who responded to treatment – how much time was there until the treatment stopped working?
5. How long did people live in this study?

What kind of study was this?

This study was a 'Phase 1' and 'Phase 2' study, which means that this was one of the first studies looking at cobimetinib on its own and together with venetoclax, and together with venetoclax and atezolizumab.

In the 'Phase 1' part of the study, a small number of people with relapsed or refractory multiple myeloma took cobimetinib with venetoclax or cobimetinib with venetoclax and atezolizumab, and the researchers did regular medical checks on the people who took part to find out more about these medicine combinations.

In the 'Phase 2' part of the study, people with relapsed or refractory multiple myeloma either took cobimetinib on its own, cobimetinib with venetoclax, or cobimetinib with venetoclax and atezolizumab. This was to find out about the safety of these medicine combinations, and to see if they worked to change the amount of cancer present or to make the cancer better during the study.

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, all other aspects of care were the same between the groups.

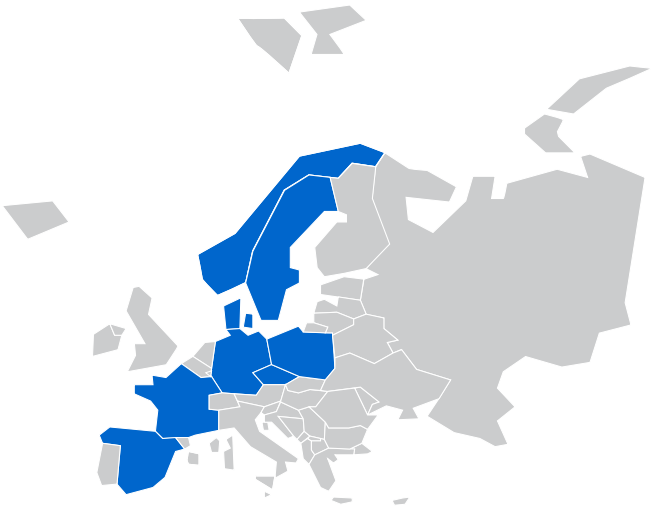
This was an 'open label' study. This means that both the people taking part in the study and the study doctors knew which of the study medicines people were taking.

When and where did the study take place?

The study started in November 2017 and finished in May 2021. This summary was written after the study had ended.

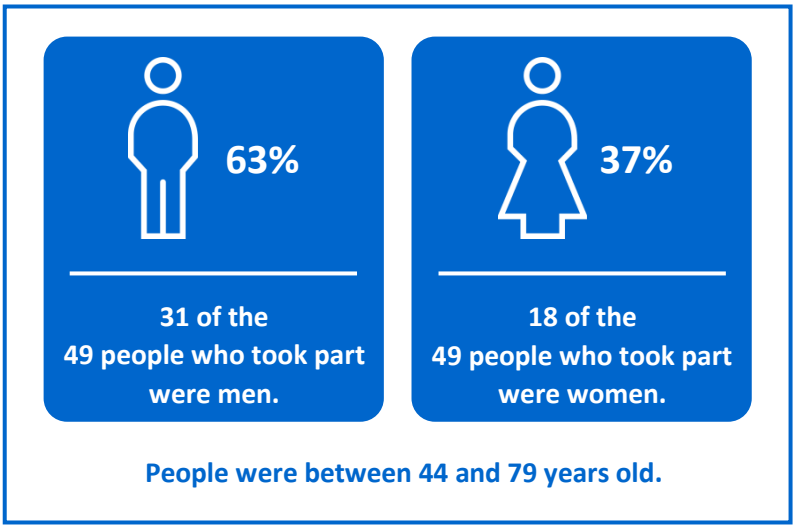
The study took place at 16 study centers – across 8 countries in Europe.
The following map shows the countries where this study took place.

- Czech Republic
- Denmark
- France
- Germany
- Norway
- Poland
- Spain
- Sweden



2. Who took part in this study?

In this study, **49 people with multiple myeloma** took part.



People could take part in the study if:

- They had multiple myeloma that had relapsed or was refractory.
- They had a life expectancy of at least 12 weeks.
- They had an Eastern Cooperative Oncology Group (also known as 'ECOG') performance score between 0 and 2, which means that they were still able to care for themselves but couldn't carry out any work activities.

People could not take part in the study if:

- They had been treated with an anti-cancer medicine within 14 days before taking part in the study.
- They had previously had an allogeneic stem cell transplant or a solid organ transplant.
- They had previously taken a medicine that worked in a similar way to cobimetinib, venetoclax, or atezolizumab.

3. What happened during the study?

During the randomization part of the study, people were selected by chance to get one of three treatments. Each round of treatments lasted 28 days. The treatments were selected at random by a computer.

The treatment groups were:

- **Cobimetinib** on its own – three tablets taken by mouth, daily for 21 days, followed by a 7-day break.
- **Cobimetinib** together with **venetoclax** – two tablets of cobimetinib taken by mouth, daily for 21 days, and eight tablets of venetoclax taken by mouth, daily for 28 days.
- **Cobimetinib** together with **venetoclax** and **atezolizumab** – two tablets of cobimetinib taken by mouth, daily for 21 days; eight tablets of venetoclax taken by mouth, daily for 28 days; and a drip (infusion) of atezolizumab into a vein on day 1 and day 15 of each treatment round.

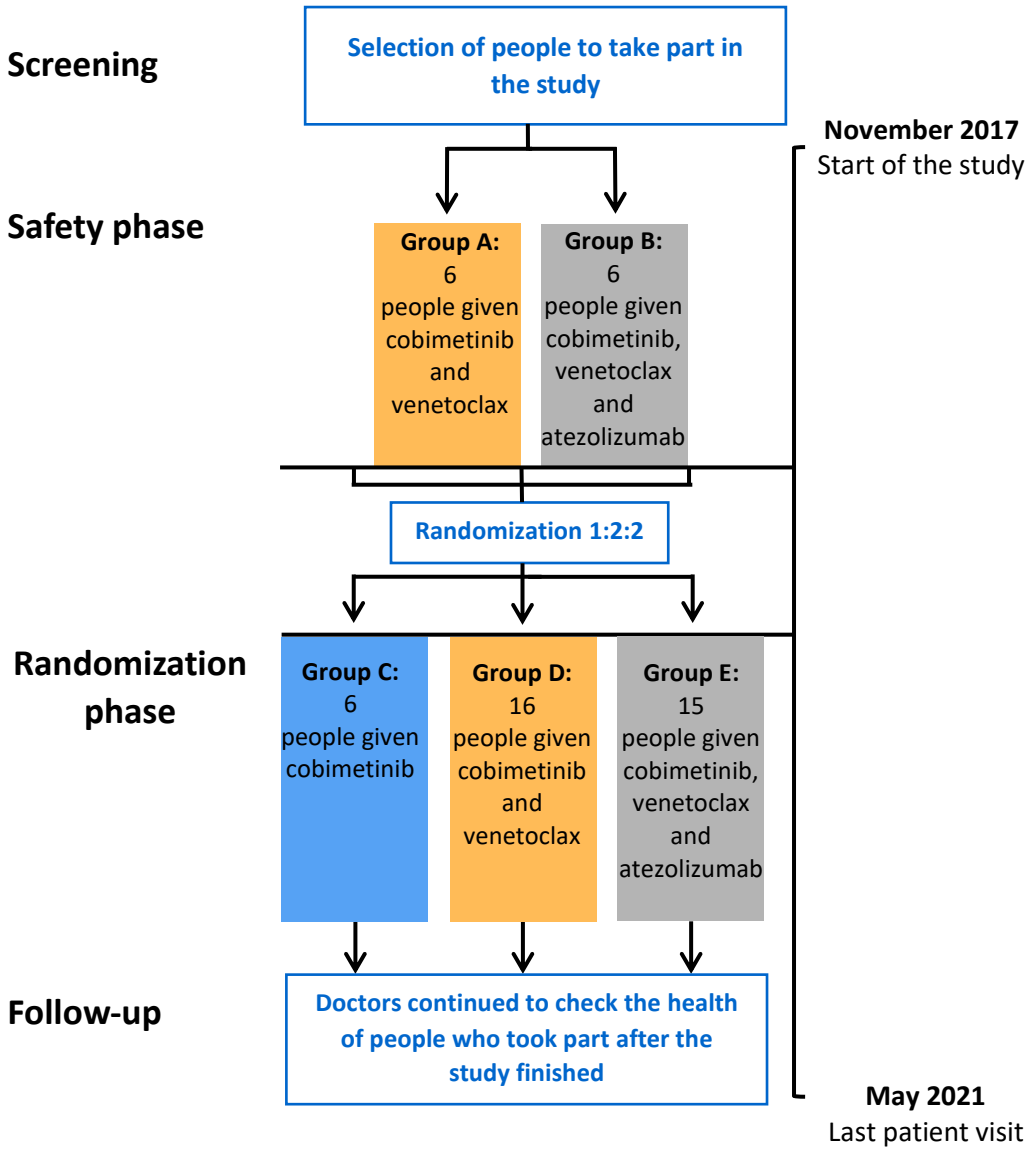
People continued to receive treatment until they had too many side effects, their disease got worse, or they stopped the study for other defined reasons.

The total length of the study, or the time from when the first patient was treated until the end of 'follow-up', was planned to last for approximately 24 months. 'Follow-up' refers to the time when the study is finished and the people who took part are asked to go back to their study center for more visits to check their overall health.

The study was split into two phases:

- **Safety phase:** this phase was to check that the amount (dose) of each medicine in the medicine combinations was safe.
- **Randomization phase:** this phase was to carry on checking that the medicines were safe, as well as checking if they worked to change the amount of cancer present, and to see how much better or worse the disease got during the study.

Look below to see more information about what happened in the study.



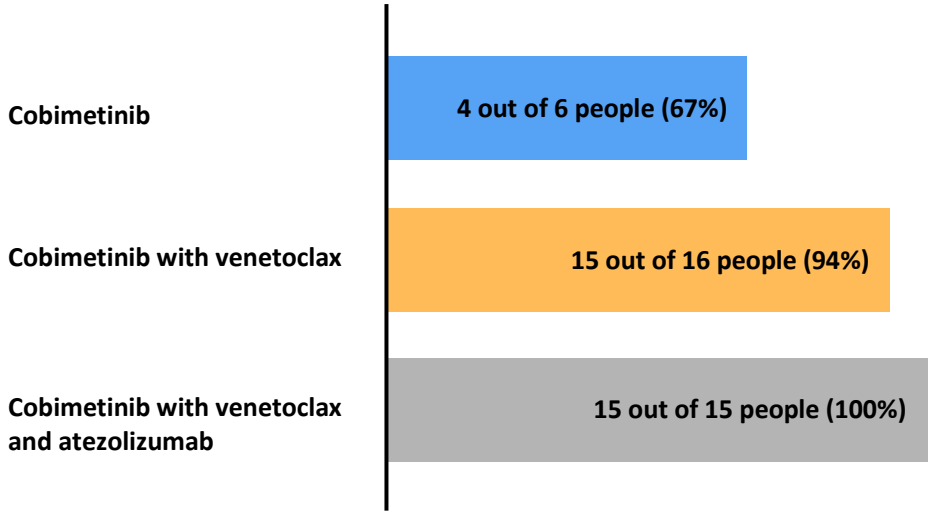
4. What were the results of the study?

Question 1: How many people had side effects (that were thought to be linked to their treatment) during the study?

Overall, most people (94%) reported side effects that were thought to be linked to their treatment:

- In the safety phase, all people (100%) reported a side effect thought to be linked to their treatment.
- In the randomization phase, over half of the people (67%) in the cobimetinib group, the majority of people (94%) in the cobimetinib with venetoclax group, and all people (100%) in the cobimetinib with venetoclax and atezolizumab group reported a side effect thought to be linked to their treatment.

How many people had side effects (that were thought to be linked to their treatment) during the randomization phase?

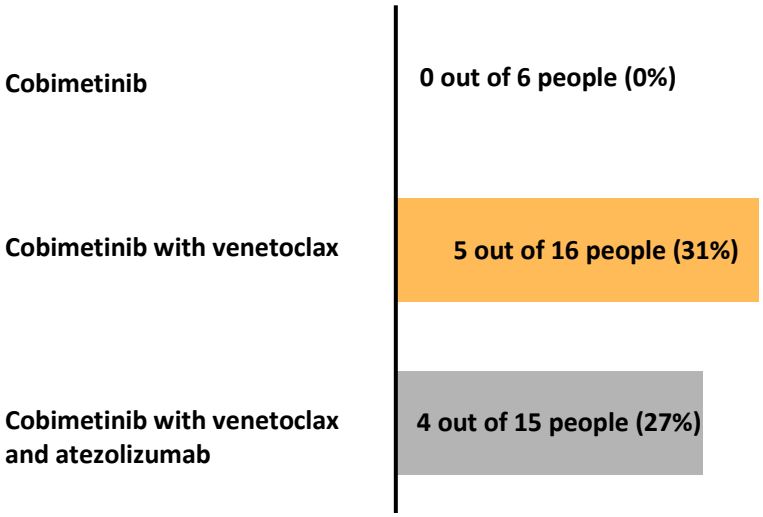


Question 2: Was there a change in the amount of cancer present, and did the cancer get better or worse during the study?

Researchers looked at whether there was a change in the amount of cancer present, and whether the cancer got better during the study, also known as 'responding to the treatment'.

- Safety phase:
  - In the group given cobimetinib with venetoclax, 17% (or 1 in 6 people) had a response to the treatment.
  - In the group given cobimetinib with venetoclax and atezolizumab, 33% (or 2 in 6 people) had a response to the treatment.
- Randomization phase:
  - In the group given cobimetinib on its own, no one (0%) responded to the treatment.
  - In the group given cobimetinib with venetoclax, 31% (or 5 in 16 people) had a response to the treatment.
  - In the group given cobimetinib with venetoclax and atezolizumab, 27% (or 4 in 15 people) had a response to the treatment.

Was there a change in the amount of cancer present, and did the cancer get better during the randomization phase (how many people had a response to the treatment)?



Question 3: How much time was there between the start of the study and people's cancer getting worse?

Researchers also looked at how much time there was before people's cancer got worse.

- Safety phase:
  - In the group given cobimetinib with venetoclax, everyone's cancer got worse. This happened after around 2 months.
  - In the group given cobimetinib with venetoclax and atezolizumab, everyone's cancer got worse. This happened after around 3 months.
- Randomization phase:
  - In the group given cobimetinib on its own, everyone's cancer got worse. This happened after around 3 months.
  - In the group given cobimetinib with venetoclax, 14 people's cancer got worse. This happened after around 5 months.
  - In the group given cobimetinib with venetoclax and atezolizumab, 11 people's cancer got worse. This happened after around 4 months.

Question 4: For people who responded to treatment – how much time was there until the treatment stopped working?

Researchers looked at people who responded to treatment, and recorded how long it took for their treatment to stop working.

- Safety phase:
  - In the group given cobimetinib with venetoclax, 1 person responded to treatment before treatment stopped working. This took around 12 months.
  - In the group given cobimetinib with venetoclax and atezolizumab, 2 people responded to treatment before treatment stopped working. This took around 5 months.

- Randomization phase:
  - In the group given cobimetinib on its own, no patients responded to the treatment.
  - In the group given cobimetinib with venetoclax, 5 people responded to treatment before treatment stopped working. This took around 15 months.
  - In the group given cobimetinib with venetoclax and atezolizumab, 4 people responded to treatment before treatment stopped working. Researchers couldn't estimate how long this took.

Question 5: How long did people live in this study?

During the study, researchers also measured how long people lived for.

- Safety phase:
  - In the group given cobimetinib with venetoclax, people lived for around 11 months.
  - In the group given cobimetinib with venetoclax and atezolizumab, people lived for around 14 months.
- Randomization phase:
  - In the group given cobimetinib on its own, people lived for around 13 months.
  - In the group given cobimetinib with venetoclax, people lived for around 14 months.
  - In the group given cobimetinib with venetoclax and atezolizumab, people lived for around 22 months.

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 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 only. Therefore, the side effects shown here may be different from those seen in other studies, or those that appear on the medicine leaflets.
- Common and serious side effects are listed in the next sections.

Most common side effects

The most common side effects are shown in the following table – these are the most common side effects across all treatment groups which occurred in over 25% of people in at least one of the treatment groups. 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 taking cobimetinib** (6 people in total)	**People taking cobimetinib with venetoclax** (16 people in total)	**People taking cobimetinib with venetoclax with atezolizumab** (15 people in total)
Diarrhea	33% (2 out of 6)	81% (13 out of 16)	87% (13 out of 15)
Feeling sick (nausea)	17% (1 out of 6)	31% (5 out of 16)	67% (10 out of 15)
Being sick (vomiting)	0% (0 out of 6)	38% (6 out of 16)	27% (4 out of 15)
Feeling tired	17% (1 out of 6)	56% (9 out of 16)	60% (9 out of 15)
Low level of white blood cells	0% (0 out of 6)	19% (3 out of 16)	53% (8 out of 15)
Low level of the blood cell fragments that help blood to clot – called ‘platelets’	0% (0 out of 6)	31% (5 out of 16)	33% (5 out of 15)
Infection in the lungs called ‘pneumonia’	0% (0 out of 6)	38% (6 out of 16)	13% (2 out of 15)
High temperature (fever)	0% (0 out of 6)	25% (4 out of 16)	20% (3 out of 15)
Rash	50% (3 out of 6)	6% (1 out of 16)	33% (5 out of 15)
Dry skin	0% (0 out of 6)	6% (1 out of 16)	33% (5 out of 15)

During this study, most people (94%) had a side effect that was thought to be related to their treatment.

In the safety phase:

- Everyone (100%) taking cobimetinib with venetoclax had a side effect.
- Everyone (100%) taking cobimetinib with venetoclax and atezolizumab had a side effect.

In the randomization phase:

- Around 67% of people taking cobimetinib on its own had a side effect.
- Around 94% of people taking cobimetinib with venetoclax had a side effect.
- Everyone (100%) taking cobimetinib with venetoclax and atezolizumab had a side effect.

Serious side effects

A side effect is considered 'serious' if it is life-threatening, needs hospital care, or causes lasting problems.
The most common serious side effects that occurred after treatment began are shown in the following table – these are the most common serious side effects across all treatment groups, that occurred in over 10% of people in at least one of the treatment groups. Some people had more than one side effect – this means that they are included in more than one row in the table.

Serious side effects reported in this study that occurred after treatment began	**People taking cobimetinib** (6 people in total)	**People taking cobimetinib with venetoclax** (16 people in total)	**People taking cobimetinib with venetoclax and atezolizumab** (15 people in total)
Blood vessel rupture affecting an important part of the brain	17% (1 out of 6)	0% (0 out of 16)	0% (0 out of 15)
Infection of the blood	17% (1 out of 6)	0% (0 out of 16)	0% (0 out of 15)
Infection caused by a bacteria called 'pneumococcus'	17% (1 out of 6)	0% (0 out of 16)	0% (0 out of 15)
Low levels of oxygen in the lungs	17% (1 out of 6)	0% (0 out of 16)	0% (0 out of 15)
Infection of the blood	17% (1 out of 6)	0% (0 out of 16)	0% (0 out of 15)
Infection in the lungs called 'pneumonia'	0% (0 out of 6)	25% (4 out of 16)	13% (2 out of 15)
Low level of the blood cell fragments that help blood to clot – called 'platelets'	0% (0 out of 6)	13% (2 out of 16)	7% (1 out of 15)
Large amount of tumor cells killed off and released in the blood	0% (0 out of 6)	13% (2 out of 16)	0% (0 out of 15)
Low level of white blood cells	0% (1 out of 6)	6% (1 out of 16)	13% (2 out of 15)

During this study, under half (45%) of all people had at least one serious side effect that was thought to be related to treatment.
In the safety phase:

- No one (0%) taking cobimetinib with venetoclax had a serious side effect.
- Half (50%) of people taking cobimetinib with venetoclax and atezolizumab had a serious side effect.

In the randomization phase:

- Around 17% of people taking cobimetinib on its own had a serious side effect.
- Around 56% of people taking cobimetinib with venetoclax had a serious side effect.
- Around 60% of people taking cobimetinib with venetoclax and atezolizumab had a serious side effect.

There were 4 people in the study who died due to side effects that may have been related to the study medicines:
In the safety phase:

- In the cobimetinib with venetoclax group, 1 out of 6 people (17%) died due to side effects that may have been related to the study medicines.

In the randomization phase:

- In the cobimetinib group, 2 out of 6 people (33%) died due to side effects that may have been related to the study medicines.
- In the cobimetinib with venetoclax and atezolizumab group, 1 out of 15 people (7%) died due to side effects that may have been related to the study medicines.

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

- In the cobimetinib with venetoclax group, 1 out of 6 people (17%) stopped taking their medicine.
- In the cobimetinib with venetoclax and atezolizumab group, 1 out of 6 people (17%) stopped taking their medicine.

In the randomization phase:

- In the cobimetinib group, 1 out of 6 people (17%) stopped taking their medicine.
- In the cobimetinib with venetoclax group, 3 out of 16 people (19%) stopped taking their medicine.
- In the cobimetinib with venetoclax and atezolizumab group, 2 out of 15 people (13%) stopped taking their medicine.

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.

6. How has this study helped research?

The information presented here is from a single study of 49 people with a type of cancer that affects the bone marrow in various parts of the body – called 'multiple myeloma'. These results helped researchers learn more about multiple myeloma and some potential medicine combinations that may be used to treat it.

As this was a Phase 1 and 2 study, the results presented in this summary have come from looking at a small group of people. More studies need to be done for researchers to have a better idea of how safe the medicine combinations are and how well they work in a larger group.

Overall, the side effects of the combinations of cobimetinib with venetoclax, and cobimetinib with venetoclax and atezolizumab were generally manageable and were similar to those experienced by people taking the individual medicines in other studies. The medicine combinations were also shown to work somewhat well in people with relapsed or refractory multiple myeloma, whereas cobimetinib on its own was less helpful at treating the cancer.

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 treatment.**

7. Are there plans for other studies?

At the time of writing this summary, no more studies looking at cobimetinib on its own, cobimetinib with venetoclax, or cobimetinib with venetoclax and atezolizumab for multiple myeloma are planned at the current time.

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/NCT03312530
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-000830-68
- https://forpatients.roche.com/en/trials/cancer/multiple-myeloma/a-study-of-cobimetinib-administered-as-single-agent-and-in-combi.html
- https://ash.confex.com/ash/2020/webprogram/Paper135845.html

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/multiple-myeloma/a-study-of-cobimetinib-administered-as-single-agent-and-in-combi.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 organized and paid for this study?

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. 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

The full title of this study is: “Phase Ib/II Study of Cobimetinib Administered as Single Agent and in Combination With Venetoclax, With or Without Atezolizumab, in Patients With Relapsed and Refractory Multiple Myeloma”.

- The protocol number for this study is: BO39813.
- The ClinicalTrials.gov identifier for this study is: NCT03312530.
- The EudraCT number for this study is: 2017-000830-68.