

Clinical Trial Results – Layperson Summary

Study of atezolizumab with cobimetinib in people with *BRAF*^{V600} wild-type melanoma who had progressed on anti-PD-1 therapy: summary of the clinical trial cohorts A and B

ClinicalTrials.gov study title: a phase Ib study evaluating cobimetinib plus atezolizumab in patients with advanced *BRAF*^{V600} wild-type melanoma who have progressed during or after treatment with anti-PD-1 therapy and atezolizumab monotherapy in patients with previously untreated advanced *BRAF*^{V600} wild-type melanoma

About this summary

This summary of the Phase 1b clinical trial (NCT03178851) was prepared to provide study participants and members of the public with information on why the study was done and the main results.

This summary is based on information known at the time of writing (March 2021). More information may now be known.

The people who took part in the study got different treatments in different groups; these different groups were called 'cohorts'. This summary is about people in cohorts A and B of the trial. People in cohort C received different study treatments, so a different summary has been written. The study started in June 2017 and finished in September 2020.

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

1. General information about this study
2. Who took part in this study?
3. What happened during the study?
4. What were the results of the study?
5. What were the side effects?
6. How has this study helped research?
7. Are there plans for other studies?
8. Where can I find more information?

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about a type of skin cancer called 'melanoma' and to learn more about the study medicine.

F. Hoffmann-La Roche Ltd, the sponsor of this study, would like to thank the participants for their contribution. If you have any questions about treatment options in your country, please speak with your doctor.

Key information about this study

- This study assessed the effects and safety of combining atezolizumab with cobimetinib in patients with advanced *BRAF* wild-type melanoma whose cancer got worse during or after treatment with immunotherapy (anti-PD-1) therapy.
- In this study, people were given a study medicine called 'atezolizumab' combined with a medicine called 'cobimetinib'. The difference between cohorts A and B was whether the two medicines were started at the same time or not.
- These study cohorts included 103 people in Australia, Spain, and the United States.
- The main finding was that the combination of atezolizumab + cobimetinib was 'active' in patients with advanced *BRAF* wild-type melanoma whose cancer got worse during or after treatment with anti-PD-1 therapy. This means that the drugs had an effect on the patients' cancer.
- Almost all patients (99%) had side effects from the study drugs.
- This study is now finished and this document provides a summary of the final analysis.

1. General information about this study

Why was this study done?

Melanoma is a type of skin cancer. There are different types of melanoma but more than half of melanoma cases are linked to mutations in the *BRAF* gene. Some people with melanoma have *BRAF* genes that have no mutations, these people are said to have *BRAF* wild-type melanoma. Knowing the characteristics of the cancer can help doctors decide which treatments are likely to be successful.

Currently, people with advanced *BRAF* wild-type melanoma are given medicines to encourage the body's immune system to attack the tumours. This is called immunotherapy. However, these treatments do not work for some patients, and their cancer gets worse during or after immunotherapy. New therapies that combine two or more treatments are being developed to treat these patients.

This study included people with advanced *BRAF* wild-type melanoma, who had previously received immunotherapy treatment for melanoma, but whose cancer had become worse.

What were the study medicines?

In this study, a new cancer immunotherapy called atezolizumab was given to patients. Atezolizumab works by blocking a pathway called PD-1/PD-L1. This allows the body's own immune cells to become active and fight the cancer cells.

Atezolizumab was studied in combination with cobimetinib. Cobimetinib is a type of cancer therapy that targets an enzyme known as MEK, which has effects on the cancer that can help atezolizumab to work better.

What did researchers want to find out?

Researchers wanted to see if the combination of atezolizumab + cobimetinib would work to stop the cancer from getting worse or prolong a patient's life (see section 4 "What were the results of the study?"). The study also looked at the safety (the side effects associated with a drug or treatment) of this combination of drugs (see section 5 "What were the side effects?").

The objective of the study in cohorts A and B was to see how well atezolizumab + cobimetinib worked as treatment for patients whose cancer got worse during or after receiving immunotherapy for their melanoma. This will help to decide if atezolizumab + cobimetinib could be offered as treatment and whether it should be tested in bigger trials with more patients.

The main questions that researchers wanted to answer were:

1. How well does atezolizumab + cobimetinib work to stop cancer growth?

The researchers measured how patients' cancer changed during treatment with the medicines. They monitored patients' cancer to see whether they got better or worse during treatment with the study medicines.

They worked out how many patients' cancer got better during this time, including people whose cancer went away completely as well as people whose cancer got a bit better. This is known as the overall response rate.

They also counted how many patients' cancer got better or stayed the same. This is called the disease control rate.

2. How long did the drug last inside the body? Did the patients' immune systems respond to the drugs?

The researchers measured how much of the drug was still in patients' blood at different times, and whether the patients' immune systems were reacting against the medicine. This will help researchers to figure out when and how much of the drug to give in the future.

3. How many people had side effects during the study, and how many were serious?

Side effects are unwanted medical problems that happen during a study. The researchers looked at what side effects happened and how bad they were, to help learn more about the safety of the study medicines.

What kind of study was this?

This study was a 'Phase 1b' study. This means that the combination of atezolizumab + cobimetinib has previously been tested in healthy people. In this study, the drugs are now being given to people with advanced melanoma whose cancer got worse during or after receiving immunotherapy. People in the two study cohorts received the drugs at different times, which will help researchers to find out the schedule that works best.

People in cohort A started taking atezolizumab + cobimetinib at the same time. People in cohort B started taking cobimetinib 2 weeks before starting atezolizumab.

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

2. Who took part in the study?

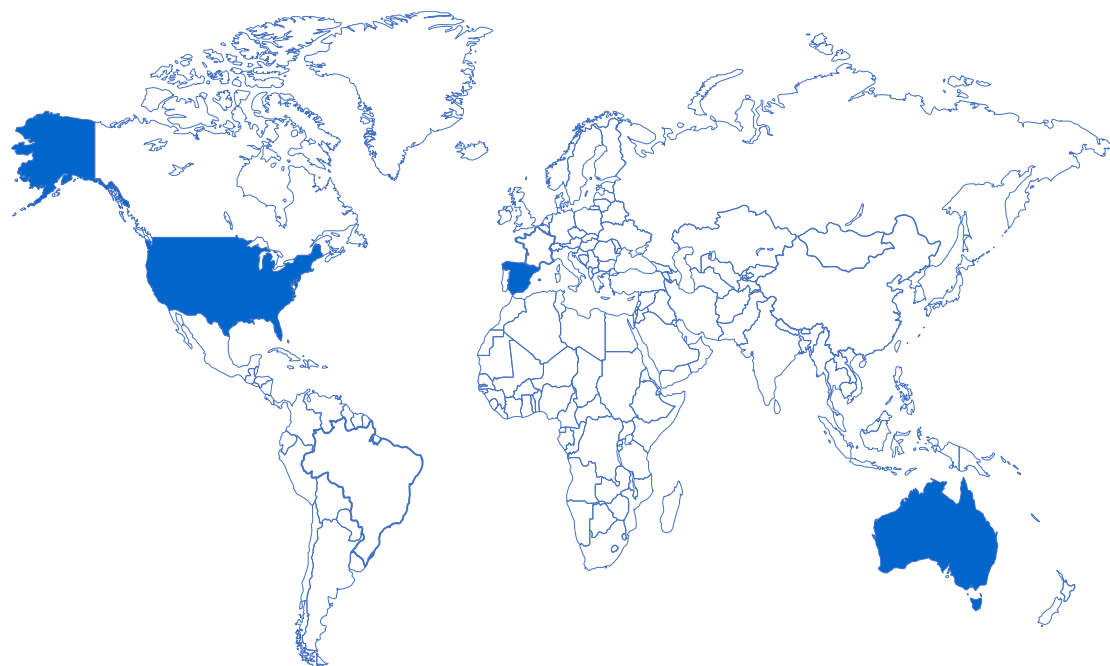
The study started in June 2017 and this summary includes the final results of the study, up to September 2020.

People could take part in the study if they met all of the following conditions:

- Aged older than 18 years
- Diagnosed with *BRAF*^{V600} wild-type melanoma
- Had previously received immunotherapy (anti-PD-1 therapy) and their cancer got worse during or after immunotherapy
- Fully physically active or restricted in physically strenuous activity only (ECOG PS 0–1)
- Had not been diagnosed with ocular melanoma, a type of cancer that develops in and around the eye
- Did not have any other active cancer that had spread from the original tumour within the last 3 years.

The people who took part in the study were an average of 65 years old, and 7 out of 10 people involved were male.

The study took place at 18 study centres across Australia, Spain and the United States. This map shows the countries where the study took place.



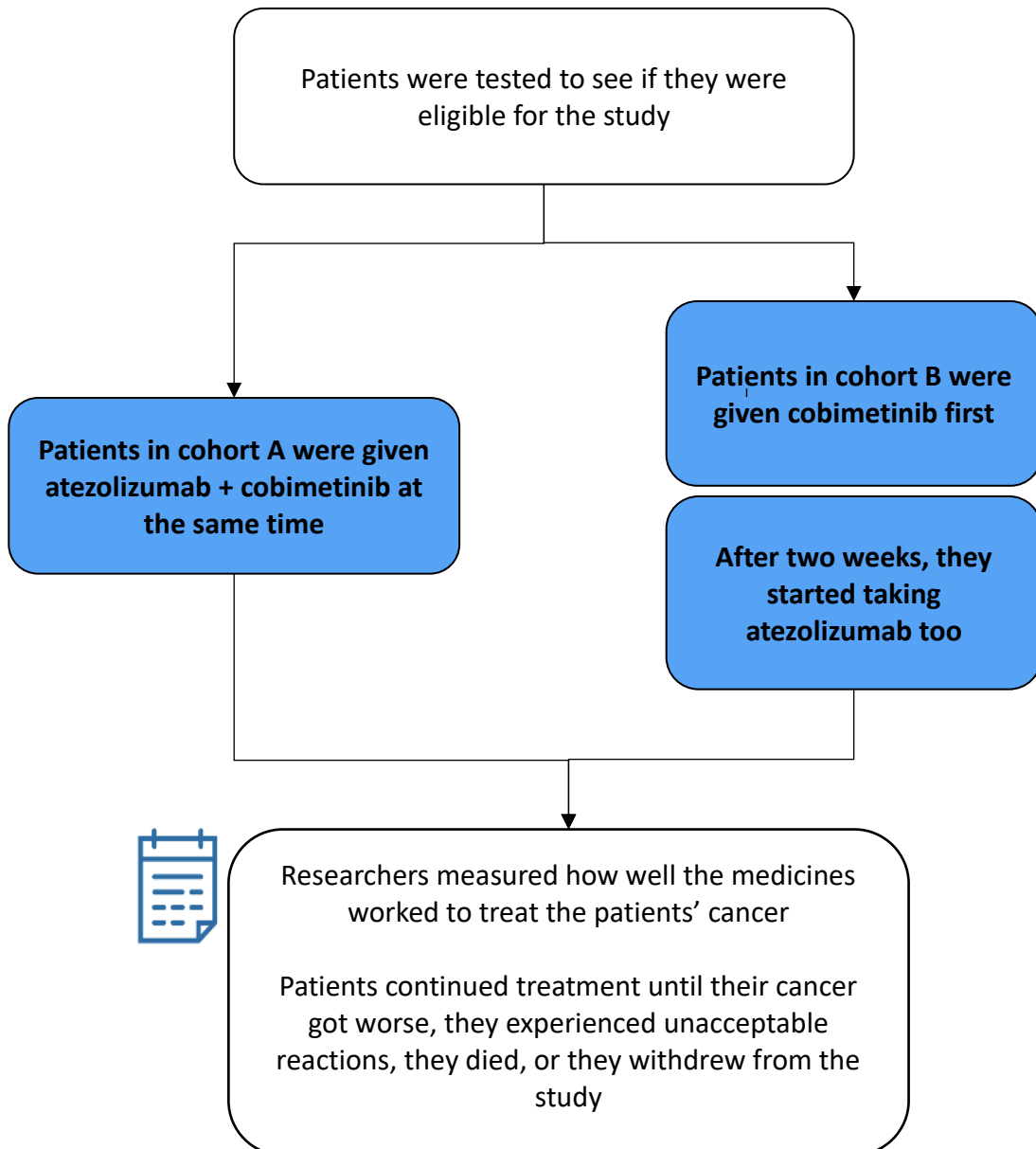
- Australia
- Spain
- United States of America

3. What happened during the study?

All patients in cohorts A and B received atezolizumab + cobimetinib.

- **Cobimetinib:** Cobimetinib 60 mg tablet taken by mouth once a day, on a 21 days on, 7 days off schedule.
- **Atezolizumab:** Atezolizumab 840 mg was given by drip (infusion) into a vein once every 2 weeks. People in cohort A started atezolizumab at the same time as cobimetinib. People in cohort B started cobimetinib and then waited 2 weeks before starting atezolizumab.

Patients continued treatment until: their cancer got worse, they experienced unacceptable side effects, they died, they became pregnant, or they withdrew from the study.



4. What were the results of the study?

How well does atezolizumab + cobimetinib work to stop cancer growth?

Researchers monitored patients' cancer to see whether they got better or worse during treatment with the study medicines. They worked out how many patients' cancer got better during this time. This is known as the overall response rate.

Out of a total of 103 people in the study cohorts, 15 peoples' cancer got better during the study, so the overall response rate was 15%. A total of 40 peoples' cancer did not get worse during the study, so the disease control rate was 39%.

Out of the 92 people in cohort A, 11 peoples' cancer got better during treatment. This means that the overall response rate in cohort A was 12%. Out of the 11 people in cohort B, 4 peoples' cancer got better. This means that the overall response rate in cohort B was 36%.

In cohort A, 34 peoples' cancer did not get worse during treatment, so the disease control rate was 37%. In cohort B, 6 peoples' cancer did not get worse, so the disease control rate was 55%.

These results mean that atezolizumab + cobimetinib was active in patients with *BRAF* wild-type advanced melanoma whose cancer got worse during or after receiving immunotherapy. This means that these medicines could be investigated in other studies of melanoma.

How long did the drug last inside the body? Did the patients' immune systems respond to the drugs?

The amount of atezolizumab + cobimetinib in the blood was similar to that found in previous studies.

For around 32% of patients, their bodies had an immune response to the medicines. There were not enough people in this study to work out if these immune responses affected how well the drugs worked. This will be investigated in future studies of the medicines.

5. What were the side effects?

Side effects (sometimes called 'adverse reactions') are unwanted medical problems that happen during a study, which may or may not be directly related to the medicines being tested in the study.

Moderate side effects are those that are not life threatening, but result in a patient needing additional treatment. Severe side effects are those that may result in death, or require or prolong time in hospital. It may be possible to reduce the number and severity of side effects by lowering the dose of medicine, or by giving the person new treatments.

The study looked at the safety of atezolizumab + cobimetinib. Researchers did this by measuring the number and type of side effects in all the people in the study.

Almost all (99%) of the patients who received atezolizumab + cobimetinib had at least one side effect related to treatment.

A side effect is considered 'serious' if it is life threatening, needs hospital care, or causes lasting problems. In this study, 47 out of 103 patients (46%) had serious side effects.

One patient had a side effect that resulted in death. In total, 22 (21%) people in cohorts A and B decided to stop taking one or both medicines because of side effects.

6. How has this study helped research?

The information presented here is a study cohort of 103 people with advanced *BRAF* wild-type melanoma whose cancer got worse on during or after receiving immunotherapy. These results helped researchers to learn more about melanoma cases and how they link to mutations in the *BRAF* gene. They also help researchers to understand more about the effects of combining atezolizumab and cobimetinib.

The results in this summary are only relevant to people with advanced *BRAF* wild-type melanoma whose cancer got worse during or after receiving immunotherapy.

The combination of atezolizumab + cobimetinib was shown to be active in patients with advanced *BRAF* wild-type melanoma whose cancer got worse during or after receiving immunotherapy. Around 15% of patients' cancer got better with the study medicines, and around 39% of patients' cancers did not get any worse.

Researchers monitored how long the medicines stayed in patients' blood. These results matched what was expected, and should help researchers to figure out when to give people the medicines. Some patients had an immune response to the study medicine. It was not possible to assess whether this affected how well the medicines worked in this study due to the small number of patients involved. This is being investigated further.

The safety of atezolizumab + cobimetinib was similar to previous studies. Almost all patients had side effects from the study medicines, but most people were able to manage these side effects.

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?

Other studies looking at the effects and safety of atezolizumab + cobimetinib are taking place.

8. Where can I find more information?

You can find more information about this study on these websites:

- <https://clinicaltrials.gov/ct2/show/NCT03178851>
- <https://forpatients.roche.com/en/trials/cancer/skin-cancer/cobimetinib--targeted-therapy--plus-atezolizumab--immunotherapy-.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/skin-cancer/cobimetinib--targeted-therapy--plus-atezolizumab--immunotherapy-.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 study evaluating cobimetinib plus atezolizumab in patients with advanced *BRAF*^{V600} wild-type melanoma who have progressed during or after treatment with anti-PD-1 therapy and atezolizumab monotherapy in patients with previously untreated advanced *BRAF*^{V600} wild-type melanoma

- The protocol number for this study is: CO39721
- The ClinicalTrials.gov identifier for this study is: NCT03178851
- The EudraCT number for this study is: 2016-004402-34