Clinical Trial Results – Layperson Summary

Study of cobimetinib with atezolizumab compared to pembrolizumab in people with *BRAF*^{V600} wild-type melanoma: summary of the clinical trial

ClinicalTrials.gov study title: A Phase III, open-label, multicenter, two-arm, randomised study to investigate the efficacy and safety of cobimetinib plus atezolizumab versus pembrolizumab in patients with previously untreated advanced *BRAF*^{V600} wild-type melanoma.

About this summary

This summary of the Phase 3 clinical trial called IMspire170 (NCT03273153) was prepared to provide study participants and members of the public with information on why the study was done and the main results so far.

This summary is based on information known at the time of writing (March 2020). More information may now be known.

The study started in December 2017 and all the people in the study had begun treatment by January 2019. At the time of writing, the IMspire170 study is still ongoing. Final results are expected after all patients have transitioned off the study and the study has ended. This is expected by the end of 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

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 untreated advanced *BRAF* wild–type melanoma.
- In this study, people were given either the study medicine called 'atezolizumab' combined with a medicine called 'cobimetinib' or an existing medicine pembrolizumab. It was decided by chance which treatment each person was given.
- This study included 446 people in 15 countries.
- The main finding was that patients with advanced *BRAF* wild-type melanoma who received atezolizumab and cobimetinib did not live longer before their cancer got worse than those who received pembrolizumab.
- Around 44% of people (97 out of 220) taking atezolizumab and cobimetinib had serious side effects, compared to around 21% of people (45 out of 216) taking pembrolizumab.
- At the time of writing this summary, the study is still happening. The study is expected to end in late 2020.

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. The V600E mutation is quite common in these cases. 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 *BRAF* wild-type melanoma are given medicines to encourage the body's immune system to attack the tumours. However, these treatments do not work for around half of patients. New therapies that combine two or more treatments are being developed as an alternative for these patients.

This study included people with advanced *BRAF* wild-type melanoma, who had not previously received treatment for melanoma.

What were the study medicines?

Pembrolizumab is an existing medicine given to people with *BRAF* wild-type melanoma with advanced disease. Pembrolizumab is an immunotherapy medication that helps shrink tumours and helps patients with advanced melanoma live longer. Pembrolizumab works by blocking a pathway called PD-1/PD-L1. This allows the immune cells to become active and be able to fight the cancer cells.

In this study, the new cancer immunotherapy medication, atezolizumab, was studied in combination with cobimetinib. Atezolizumab also works by targeting the PD-1/PD-L1 pathway, which allows immune cells to become active and fight the cancer cells. 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 compare pembrolizumab with cobimetinib + atezolizumab – to see if the combination could slow down the cancer from getting worse or prolong a patient's life compared with pembrolizumab alone (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 the two drugs when given to patients together (see section 5 "What were the side effects?").

The objective of the study was to see if atezolizumab + cobimetinib should be offered as treatment instead of pembrolizumab alone for patients who have not received any other treatment for their metastatic melanoma.

The main question that researchers wanted to answer was: How long does it take until a patient's cancer gets worse if they are taking atezolizumab + cobimetinib compared with if they are taking pembrolizumab?

The researchers measured the time between when the patients started treatment to when patients' cancers started getting worse (i.e. continued to grow or spread), or until the patient died. The time from the start of the study to when these things happen is known as progression-free survival.

The researchers also wanted to know: 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 3' study. This means that atezolizumab and cobimetinib had been tested in a smaller number of people with advanced melanoma before this study. In this study, a larger number of people with advanced melanoma either took atezolizumab + cobimetinib or pembrolizumab – this was to find out if atezolizumab in combination with cobimetinib should be offered as treatment instead of pembrolizumab alone for patients who have not received any other treatment for advanced melanoma.

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.

The study was 'randomised'. This means that it was decided by chance which of the medicines people in the study would have – like tossing a coin.

2. Who took part?

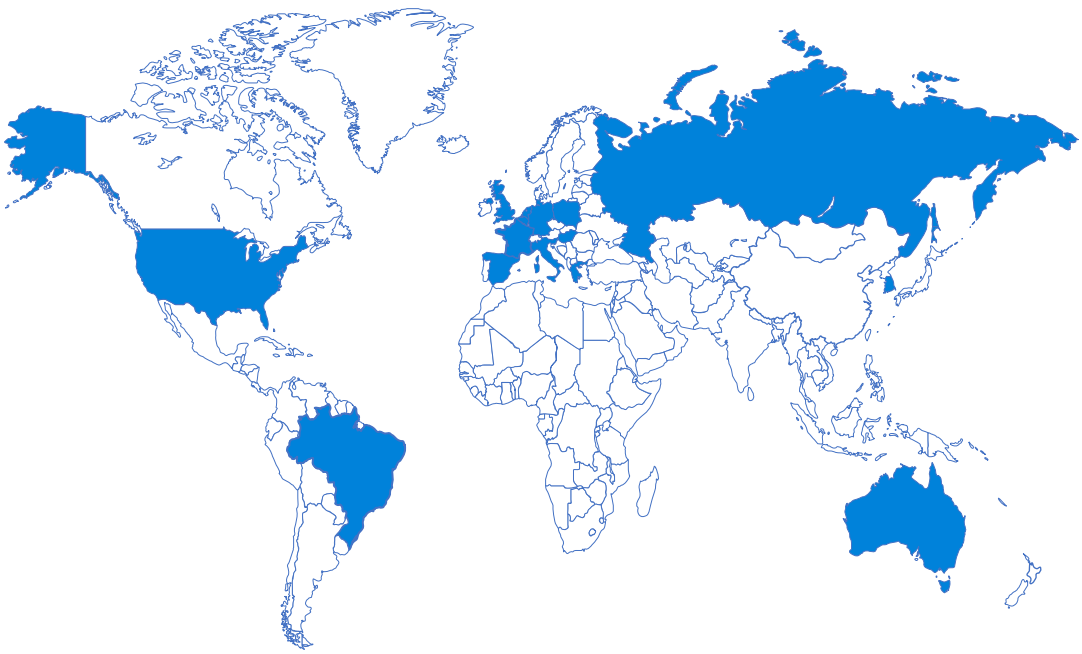
The study started in December 2017 and this summary includes the primary analysis of the study, with results up until April 2019. At the time of writing this summary, the study is still happening – this summary presents the complete results from one part of the study.

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

- Aged over 18 years
- Diagnosed with *BRAF*^{V600} wild-type melanoma
- Had not received any other anti-cancer therapy for their melanoma
- Were fully physically active or were 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 active or untreated cancer that has spread from the original tumour to the central nervous system (CNS metastases).

The people who took part in the study were an average of 66 years old, and 6 out of 10 people involved were male. These numbers were similar for the two study groups.

The study took place at 134 study centres across 15 countries in Europe, Asia, Latin America, the United States, and Australia. The following map shows the countries where this study took place.



- Australia
- Belgium
- Brazil
- France
- Germany
- Greece
- Hungary
- Italy
- Korea (Republic of)
- Netherlands
- Poland
- Russia
- Spain
- United Kingdom
- United States of America

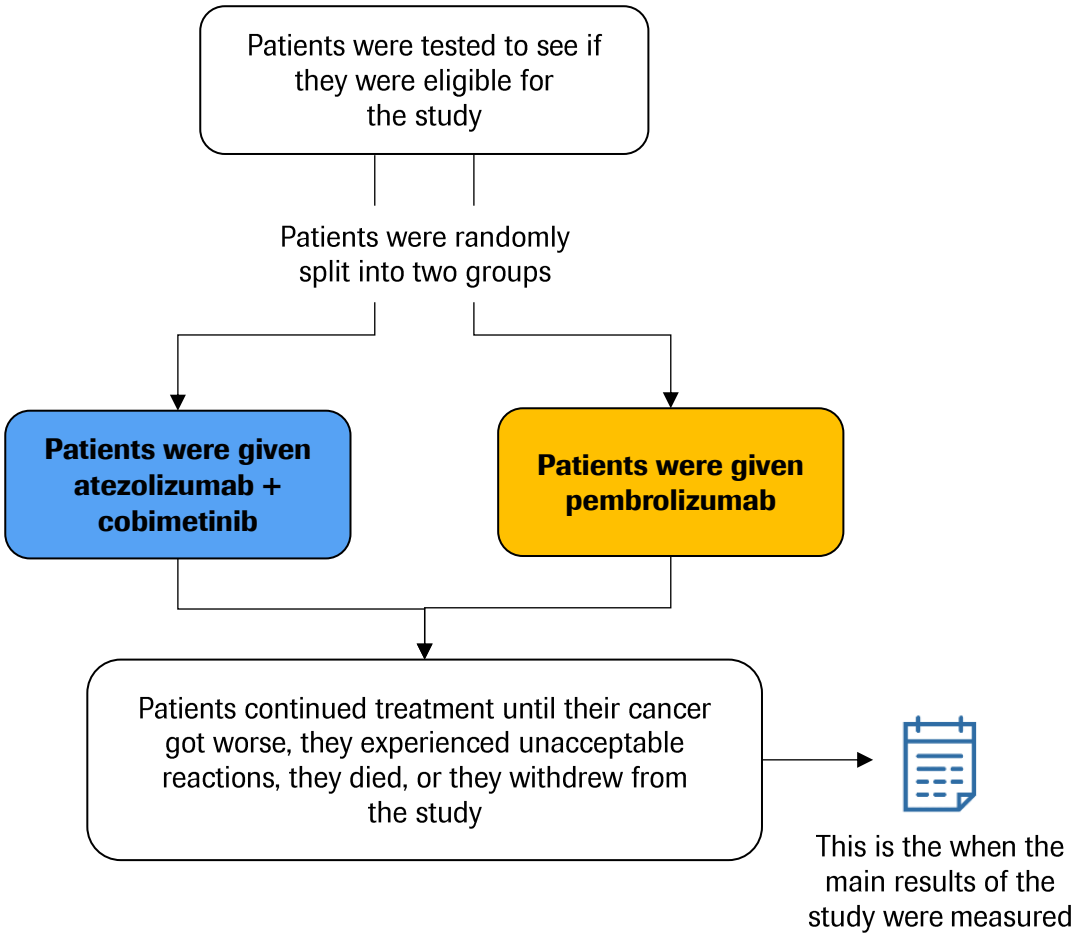
3. What happened during the study?

Patients were randomly split into two groups. The treatment groups were:

- **Atezolizumab + cobimetinib** – Cobimetinib 60 mg tablet taken by mouth once a day on a 21 days on, 7 days off schedule. Atezolizumab 840mg was given by drip (infusion) into a vein once every 2 weeks.
- **Pembrolizumab** – 200mg was given by drip (infusion) into a vein once every 3 weeks.

Patients continued treatment until: their cancer got worse, they experienced unacceptable side effects, they died, they became pregnant, or they withdrew from the study. The researchers measured the average time it took for these things to happen for people in the two groups.

This study is still happening, so some people are still being treated with the study medicines. When the study finishes, the people who took part will be asked to go back to their study centre for more visits to check their overall health.



4. What were the results of the study?

How long did patients live without their cancer getting worse?

Researchers measured how long it took from the start of treatment with atezolizumab + cobimetinib or pembrolizumab until a patient's cancer got worse, or the patient died. This is known as progression-free survival. This was assessed by the patients' doctors, as well as a group of experts called an Independent Review Committee.

It took about the same amount of time for patients' cancer to get worse in each of the two groups. When atezolizumab and cobimetinib were given to patients, it took an average of 5.5 months for their cancer to get worse. For patients who received pembrolizumab, it took 5.7 months for their cancer to get worse.

On average, how long did patients in the two groups live without their cancer getting worse?

5. What were the side effects?

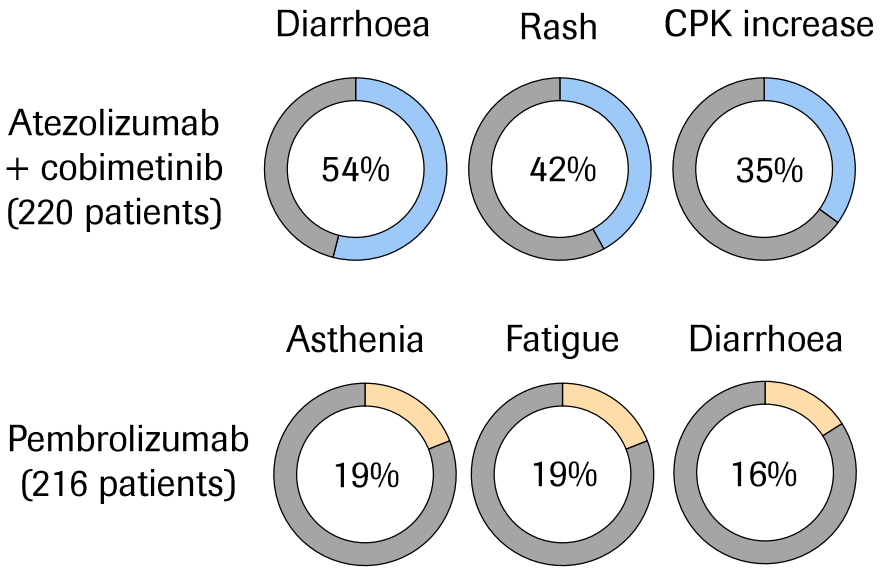
Side effects (sometimes called 'adverse reactions') are unwanted medical problems that happen during a study, which may or may not be directly related to the medicines being tested in the study.

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 trial looked at the safety of atezolizumab + cobimetinib compared with pembrolizumab. Researchers did this by measuring the number and type of side effects in all patients.

More patients who received atezolizumab + cobimetinib had side effects compared with patients who received pembrolizumab. The most common side effects in the atezolizumab + cobimetinib group included diarrhoea, rash, and muscle or heart damage (shown by higher levels of something called CPK in the blood). The most common side effects in the pembrolizumab group were overwhelming tiredness (fatigue), physical and mental weakness (asthenia), and diarrhoea.

The most common side effects in the two groups included:

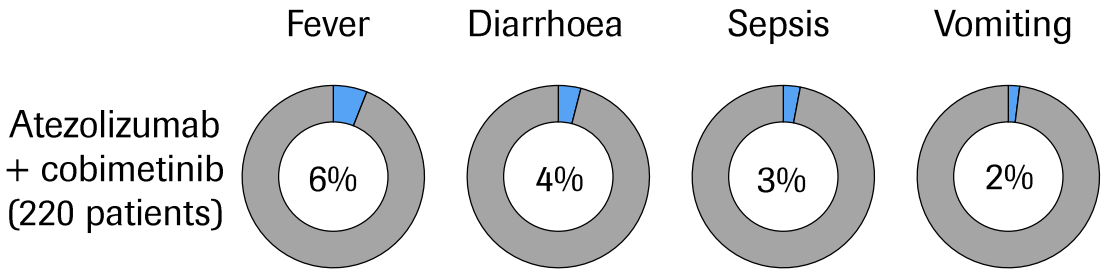


Serious side effects

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

During this study, 44 in every 100 people (44%) taking atezolizumab and cobimetinib had at least one serious side effect, compared with around 21% of people taking pembrolizumab who had a serious side effect.

The kinds of serious side effects reported by 5 or more of the 220 people (≥2%) taking atezolizumab + cobimetinib were:



No kinds of serious side effects were reported in 5 or more of the 216 people taking pembrolizumab.

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

- 3 out of 220 people (1%) in the atezolizumab + cobimetinib group
- 2 out of 216 people (1%) in the pembrolizumab group

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

- 46 out of 220 people (21%) in the atezolizumab + cobimetinib group
- 12 out of 216 people (6%) in the pembrolizumab group

6. How has this study helped research?

The information presented here is from a single study of 446 people with advanced *BRAF* wild-type melanoma. These results helped researchers learn more about melanoma cases and how they link to mutations in the BRAF gene. They also help researchers 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 who have not received any treatment for their disease.

The combination of atezolizumab and cobimetinib was not shown to be a more effective treatment than pembrolizumab on its own in patients with advanced *BRAF* wild-type melanoma. Patients who received atezolizumab and cobimetinib did not live longer before their cancer got worse than those who received pembrolizumab.

Medical signals called biomarkers are continuing to be assessed. These might help researchers understand the study results in more detail.

Patients who received atezolizumab and cobimetinib had more side effects than patients treated with pembrolizumab. The side effects that patients had were similar to those expected based on previous clinical trials.

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/results/NCT03273153
- https://forpatients.roche.com/en/trials/cancer/skin-cancer/a-study-of-cobimetinib-plus-atezolizumab-versus-pembrolizumab-in.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/a-study-of-cobimetinib-plus-atezolizumab-versus-pembrolizumab-in.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 III, open-label, multicenter, two-arm, randomised study to investigate the efficacy and safety of cobimetinib plus atezolizumab versus pembrolizumab in patients with previously untreated advanced *BRAF*^{V600} wild-type melanoma.

The study is known as 'IMspire170'.

- The protocol number for this study is: CO39722
- The ClinicalTrials.gov identifier for this study is: NCT03273153
- The EudraCT number for this study is: 2016-004387-18