

Summary of Clinical Trial Results

A study to see whether combining three drugs – atezolizumab plus bevacizumab and cobimetinib – works and is safe for people with colon or rectal cancer after chemotherapy has not worked

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 (July 2020). More information may now be known.

The study started in September 2016 and finished in June 2019. This summary was written after the study had ended.

One study can't tell us everything about the possible side effects of a medicine and how well the medicine works. It takes lots of people in many studies to learn as much as we can about a medicine. 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.**

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Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about colon or rectal cancer and about treatment with a drug called atezolizumab (the study medicine) taken with two other study medicines called bevacizumab and cobimetinib.

Key information about this study

- This study was done to:
 - See whether the combination of three study medicines, atezolizumab plus bevacizumab and cobimetinib, works (does it shrink the tumours and how long is it before the cancer gets worse?) in people with colon or rectal cancer (sometimes called bowel cancer) whose cancer got worse after taking standard chemotherapy treatment.
 - See whether the combination of atezolizumab plus bevacizumab and cobimetinib is safe in people with colon or rectal cancer (how many people had side effects?).
- The people in this study were put into one of three groups: **Group 1**, **Group 2** or **Group 3**.
 - All of the people in **Groups 1-3** took atezolizumab plus bevacizumab and cobimetinib.
 - **Group 1** was started before **Group 2** and **3** so that the doctors could first learn if this combination was safe for people.
 - People were included in **Group 2** to learn more about how this combination was handled by them and also to see how well it worked.
 - People were included in **Group 3** for the same reason as **Group 2** but also because they were willing and able to let doctors take samples from their tumour during study treatment.
- This study included 49 people in 2 countries.
- **Groups 1, 2, and 3** included different people, and their results are shown together.
- The study showed that:
 - Tumours got smaller in 5 out of 49 people in the study (or 1 out of every 10 people [10%]) in **Groups 1-3** who had been taking atezolizumab plus bevacizumab and cobimetinib for as long as almost 2 years (21 months).
 - Tumours got larger in 9 out of 49 people in the study (or 18 out of every 100 people [18%]).
 - In **Groups 1-3**, people's cancer got worse around 6 months after they had started taking atezolizumab plus bevacizumab and cobimetinib.
- In **Groups 1-3**, 33% (16 out of 49 people in the study or 33 in every 100 people) who took atezolizumab plus bevacizumab and cobimetinib for up to 2 years had at least one serious side effect (a serious side effect is any side effect that results in death, is life-threatening, needs a hospital stay or causes longer hospital stays).
- At the time of writing this summary, the study has finished (in June 2019).

1. General information about this study

Why was this study done?

People who have colon or rectal cancer (sometimes called bowel cancer) that has spread to other parts of the body are usually treated with a type of medicine called 'chemotherapy'. Doctors treat people with just chemotherapy medicines or with chemotherapy medicines and another medicine. Some of the frequently used types of chemotherapy include 5-fluorouracil, oxaliplatin, and irinotecan.

Chemotherapy is sometimes taken with a type of medicine called an 'anti-angiogenic' medicine. This type of medicine stops the cancer cells from forming the new blood vessels that they need to grow. Anti-angiogenic medicines are called 'targeted' medicines because they can tell the difference between cancer cells and normal healthy cells and they 'target' the cancer cells only. There are other types of targeted medicines that stop tumours from growing by stopping cancer cells from dividing into new cells.

Chemotherapy or targeted medicines do not work in everyone, or they may work for only a short time each time they are given and then the cancer gets worse again. Some people have to stop taking these medicines because the side effects are too bad.

These people are sometimes given a treatment called immunotherapy, which is a medicine that helps a person's own immune system to attack tumours. Like chemotherapy, immunotherapy medicines work better in some people than in others and sometimes work for only a short time. This may be because the cancer can 'hide' from the immune system and/or learn to 'escape' from the immune system's attacks.

Giving immunotherapy together with two different targeted medicines for the first time for people with colon or rectal cancer is like a 'triple attack' on the cancer. This triple attack may work better than any of the medicines on their own.

In this study, researchers wanted to see if combining an immunotherapy medicine with two different targeted medicines would shrink tumours in people with colon or rectal cancer.

Researchers also wanted to see if the combination of the three medicines is safe for people to take. The people in the study had colon or rectal cancer that had become worse after taking chemotherapy.

What were the study medicines?

This study looked at a medicine called 'atezolizumab' (known by its brand name, Tecentriq®).

- You say this as 'a - teh - zo - liz - oo - mab'.
- The body's immune system fights diseases like cancer. However, cancer cells can block (stop) the immune system from attacking the cancer. Atezolizumab releases this blockage - meaning that the immune system is able to fight the cancer cells.
- When people take atezolizumab, their tumour (cancer) may get smaller.
- This medicine is a type of immunotherapy.

In this study, atezolizumab was taken together with medicines called bevacizumab (known by its brand name Avastin®) and cobimetinib (known by its brand name Cotellic®).

- **Bevacizumab**
 - You say this as 'beh - va - si - zoo - mab'.

- Cancers grow their own blood vessels so they can get food and oxygen from the blood. The cancer needs a protein called vascular endothelial growth factor (VEGF) to do this. Bevacizumab blocks VEGF and stops the cancer from growing blood vessels, so the cancer starves and can't grow.
- This medicine is an anti-angiogenic medicine

- **Cobimetinib**

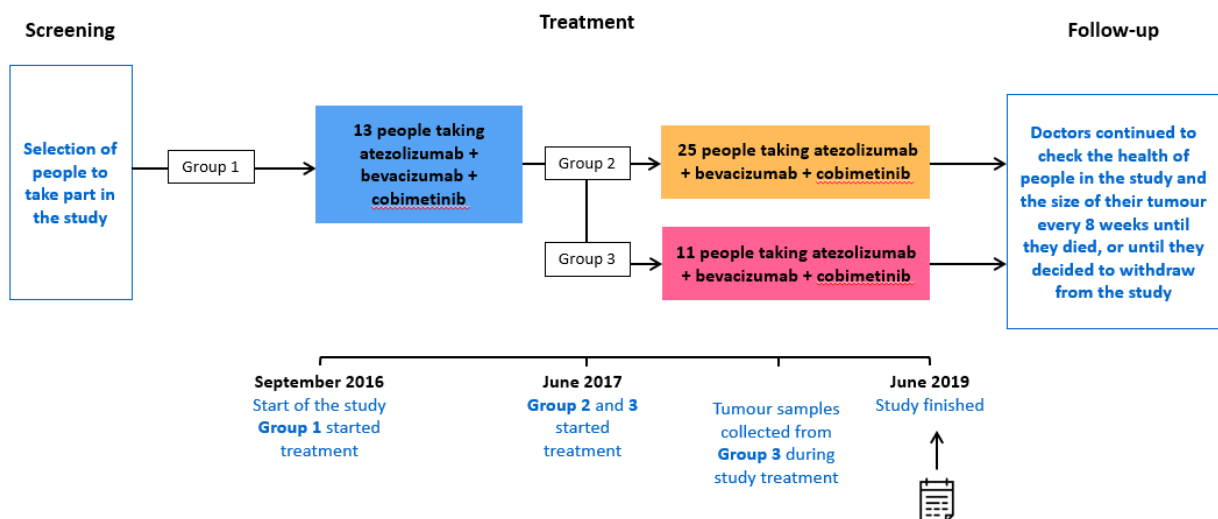
- You say this as 'koe - bi - me - ti - nib'.
- Cancers grow larger by dividing into new cells and they use proteins to help them do this. These proteins can also help the cancer to hide from the body's immune system. Cobimetinib blocks certain proteins such as mitogen-activated protein kinase 1 and 2 (MEK1 and 2) which then stops the cancers from growing and also makes them more open to attack by the immune system.
- This medicine is a targeted medicine

- Researchers gave all the people atezolizumab plus bevacizumab and cobimetinib to see if this combination would shrink tumours or stop them from growing, and to see how many people had side effects when taking these medicines together.

How the study was done

During the study:

- All the people in **Group 1** took atezolizumab plus bevacizumab and cobimetinib (starting in September 2016).
- If the combination of study medicines was safe for people in **Group 1**, people in **Group 2** and **Group 3** started taking the same combination (atezolizumab plus bevacizumab and cobimetinib) at the same dose, starting in June 2017.
 - People were included in **Group 2** to learn more about how this combination was handled by them and also to see how well it worked.
 - People were included in **Group 3** for the same reason as **Group 2** but also because they were willing and able to let doctors take samples from their tumour during study treatment. The information collected from these samples will be used to find in the tumour that could predict which people had tumours that would shrink or stop the study medicines from working.
- **Groups 1, 2, and 3** included different people and their results are shown together.
- This picture shows what happened in the study.



- This study has finished. The 📅 symbol on the timeline shows when the information in this summary was collected – in June 2019, almost 3 years after the study started. At that time, all 49 patients who took the treatment had stopped treatment because the study was stopped early by the trial sponsor, decided to leave the study early or died. When the study finished, the people who took part were asked to go back to their study centre for more visits – to check their overall health.

What did researchers want to find out?

- Researchers wanted to know whether a combination of atezolizumab plus bevacizumab and cobimetinib would make tumours shrink in people with colon or rectal cancer and/or see how long they could stay on treatment before their cancer got worse (by looking at the results of **Groups 1-3**)
 - See section 4 ‘What were the results of the study?’
- They also wanted to find out how safe this combination of study medicines was – by checking how many people had side effects when taking the three medicines together during this study (by looking at the results of **Groups 1-3**)
 - See section 5 ‘What were the side effects?’

The main questions that researchers wanted to answer were:

1. How many people in **Groups 1-3** had smaller tumours that could be measured after taking their medicine?
2. In **Groups 1-3**, how much time was there between the start of the study and people’s cancer getting worse?
3. For people whose tumours got smaller during the study in **Groups 1-3**, how much time was there until their cancer then got worse?
4. How safe was the combination of these medicines? How many people had side effects when taking the three medicines together during this study?

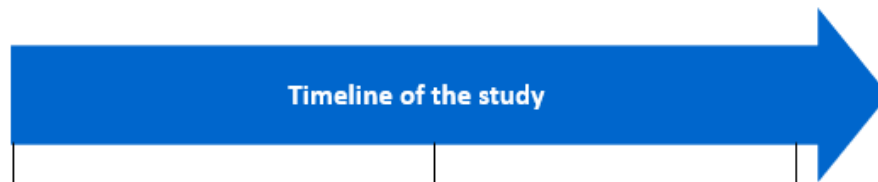
What kind of study was this?

This was a ‘Phase 1’ study, which means that this was the first study of atezolizumab taken together with bevacizumab and cobimetinib. This was also the first study of a combination of medicines in colon or rectal cancer that didn’t include chemotherapy. A small number of people with colon or rectal cancer took atezolizumab plus bevacizumab and cobimetinib, and the researchers did medical tests on the people who took part to find out more about the three-drug combination.

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

When and where did the study take place?

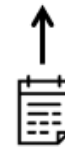
The study started in September 2016 and finished in June 2019. This summary includes the results up until June 2019.




September 2016
 Start of the study – first patient in **Group 1** is given study medicine

June 2017
 First patients in **Group 2 and 3** are given study medicine

June 2019
 The study finished

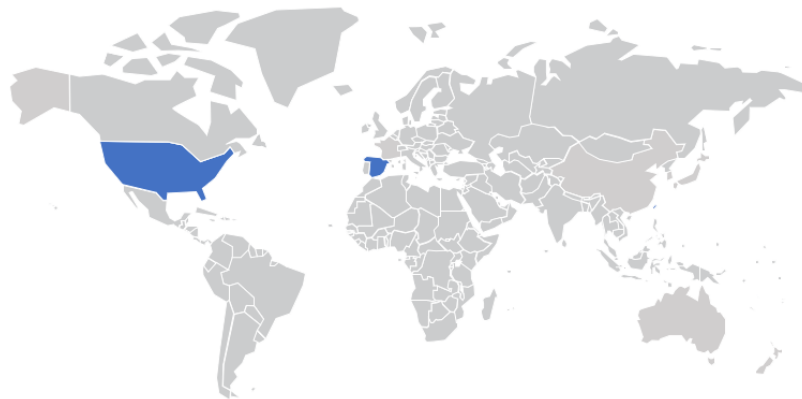


Results were collected

This study has finished. The  on the timeline shows when the information in this summary was collected – after the study finished in June 2019.

The study was done at 6 study centres in the United States and Spain.

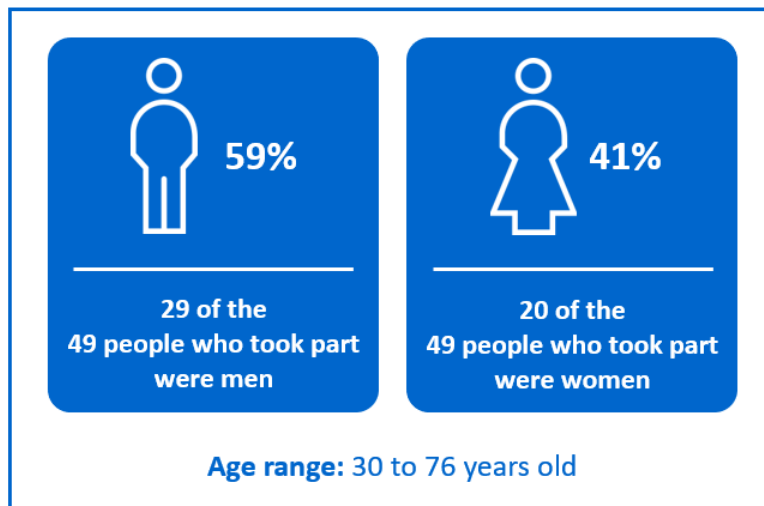
- USA
- Spain



2. Who took part in this study?

Forty-nine adults with colon or rectal cancer that had spread to other parts of their body and could not be cured with surgery took part in this study. Before they started the study, the people taking part had found that their cancer got worse after taking one or more courses of standard chemotherapy treatment that included the medicines 5-fluorouracil and oxaliplatin or irinotecan.

Here is more information about the people who took part in the study.



3. What happened during the study?

This table shows the groups in the study, the drugs they were taking and how often the drugs were taken.

	Group 1	Group 2	Group 3
Number of people taking atezolizumab plus bevacizumab and cobimetinib	13	25	11
When and how the drugs were taken	Atezolizumab and bevacizumab were injected into a vein once every 2 weeks Cobimetinib was taken by mouth every day for 21 out of every 28 days		

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

Question 1: How many people in **Groups 1-3** had smaller tumours that could be measured after taking their medicine?

Researchers collected information on how many people in **Groups 1-3** had smaller tumours up to almost 2 years (21 months) after they started taking atezolizumab plus bevacizumab and cobimetinib.

- Tumours got smaller in 5 out of 49 people in the study (or 1 out of every 10 people [10%]).
- Tumours stayed about the same size and did not grow bigger in 27 out of 49 people in the study (or 55 out of every 100 people [55%]).
- Tumours got larger in 9 out of 49 people in the study (or 18 out of every 100 people [18%]).
- None of the people had tumours that went away after treatment.

Question 2: In **Groups 1-3**, how much time was there between the start of the study and people's cancer getting worse?

In **Groups 1-3**, researchers looked at how much time there was before people's cancer got worse – this information was collected over 21 months.

- The study showed that people’s cancer got worse around 6 months after they had started taking atezolizumab plus bevacizumab and cobimetinib (some people’s cancer took longer to get worse, and some people’s cancer got worse sooner than 6 months).

Question 3: For people in **Groups 1-3** whose tumours got smaller during the study, how much time was there until their cancer then got worse?

Researchers looked at people whose tumours had become smaller during the study and recorded how long it took for people’s cancer to then get worse again. This information was collected from the start of the study until June 2019.

- For people in **Groups 1-3** who had tumours that got smaller while taking atezolizumab plus bevacizumab and cobimetinib, their cancer got worse in around 6 months (some people’s cancer took longer to get worse, and some people’s cancer got worse sooner than 6 months).

This section shows only the key results from the study at this point. You can find information about all other results at the end of this summary (see section 8).

5. What were the side effects?

Side effects are medical problems (such as being sick) that happen while people are taking a medicine. Side effects can vary from mild to very serious and may vary from person to person.

- Some side effects may be caused by the treatments in the study.
- Not all of the people in this study had all of the side effects.
- 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.

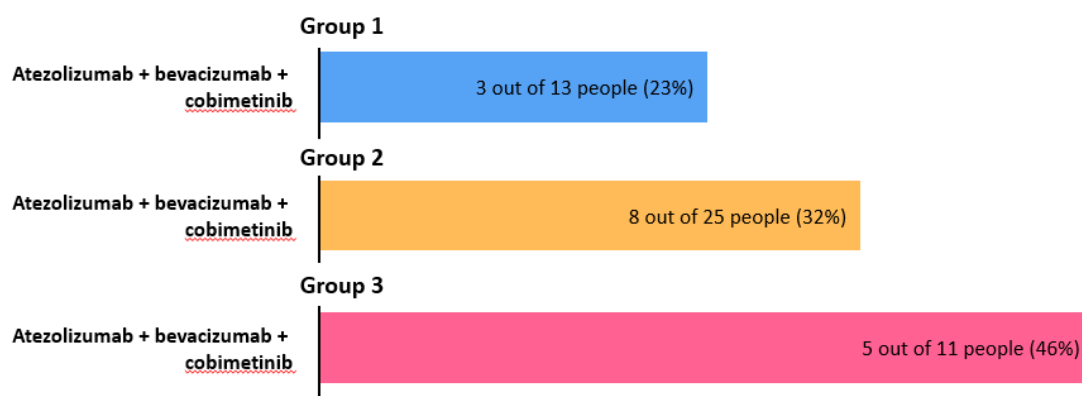
Serious and common side effects are listed in the following sections.

Serious side effects

A side effect is considered ‘serious’ if it is life-threatening, needs hospital care, results in death or causes lasting problems.

- During this study, 16 out of 49 people in the study (or 33 in every 100 people [33%]) had at least one serious side effect.
- This picture shows how many people had at least one serious side effect in each group.

How many people had at least one serious side effect?



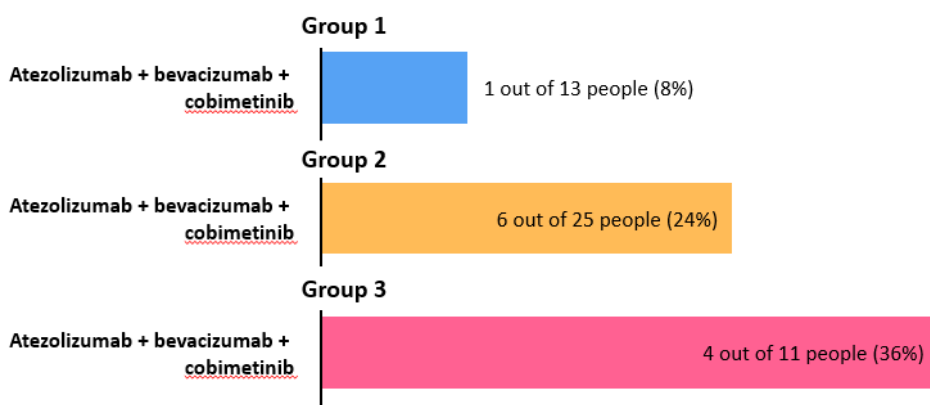
This information was collected from people in **Groups 1-3** whose health had been followed by doctors for up to 2 years.

One person in the study died due to side effects that may have been related to one of the study medicines. This was:

- 1 out of 25 people (4%) in **Group 2** who took atezolizumab plus bevacizumab and cobimetinib.
- 0 out of 13 in **Group 1** and 0 out of 11 in **Group 3** who took atezolizumab plus bevacizumab and cobimetinib.
 - This information was collected from people in **Groups 1-3** whose health had been followed by doctors for up to 2 years.

During the study, some people decided to stop taking at least one of their medicines because of side effects.

How many people decided to stop taking at least one of their medicines because of side effects?

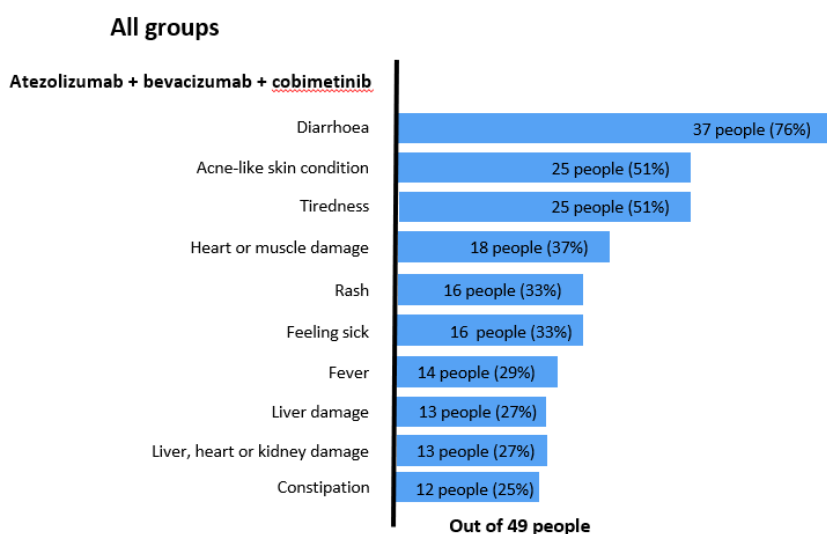


This information was collected from people in **Groups 1-3** whose health had been followed by doctors for up to 2 years.

Most common side effects

This picture shows the most common side effects are shown in the following picture. All patients experienced at least one of these side effects.

How many people had each of these 10 most common side effects?



This information was collected from people in **Groups 1-3** whose health had been followed by doctors for up to 2 years.

The side effects that people experienced in this study were the same as those experienced by people who took atezolizumab, bevacizumab or cobimetinib in other studies, or as prescribed by their doctors.

The people taking the three study medications together in this study did not experience any new or unexpected side effects, compared to people taking one of the study medicines in other studies.

Side effects thought to be caused by study medicines

During this study, most people (about 9 out of every 10 people [98%]) had a side effect that their doctors thought was caused by the study medicines they were taking (called a ‘treatment-related’ side effect).

People taking atezolizumab + bevacizumab + cobimetinib	Group 1	Group 2	Group 3
People with treatment-related side effects	92% 12 out of 13 people	100% 25 out of 25 people	100% 11 out of 11 people

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 study of 49 people with colon or rectal cancer. These results are helping researchers learn more about colon or rectal cancer and treatment with atezolizumab plus bevacizumab and cobimetinib.

- The results showed that, for most of the 49 people with colon or rectal cancer in this study, taking atezolizumab plus bevacizumab and cobimetinib did not appear to shrink their tumours. However, tumours got smaller in 1 out of every 10 people (10%) and stayed about the same size and did not grow bigger in 55 out of every 100 people (55%).
- The results also showed that it took around 6 months for people’s cancer to get worse after they had started taking the three study medicines.
- During the study, the side effects that people had while taking atezolizumab plus bevacizumab and cobimetinib were similar to those experienced by people taking the individual medicines in other studies.

One study can’t tell us everything about how safe a medicine is and how well it works. 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 moment, there are no plans for studies looking at the combination of atezolizumab plus bevacizumab and cobimetinib in people with colon or rectal cancer.

This study started in September 2016 and finished in June 2019. This summary includes the results up until June 2019.

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/NCT02876224>
- <https://forpatients.roche.com/en/trials/cancer/crc/study-of-cobimetinib-in-combination-with-atezolizumab-and-bevaci.html>

If you would like to find out more about the results of this study, the full title of the relevant abstract presented at the 2019 European Society for Medical Oncology (ESMO) congress is: “A phase Ib study of the safety and efficacy of atezolizumab (atezo) + bevacizumab (bev) + cobimetinib (cobi) in patients (pts) with metastatic colorectal cancer (mCRC)”. The authors of the scientific paper are: J. Bendell, C. Lieu, K.P.S Raghav, G. Argilés, A. Cubillo and others. The abstract from the ESMO congress is published in the journal *Annals of Oncology*, volume number 30, on pages v198-v252.

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/crc/study-of-cobimetinib-in-combination-with-atezolizumab-and-bevaci.html>
- Contact a representative at your local Roche office.

If you took part in this study and have any questions about the results:

- Speak to 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 Open-label Study Evaluation the Safety, Tolerability and Pharmacokinetics of Cobimetinib in Combination with Bevacizumab and Immunotherapy when Administered in Patients with Gastrointestinal and Other Tumors”.

- The protocol number for this study is: CO39083.
- The ClinicalTrials.gov identifier for this study is: NCT02876224.

- The EudraCT number for this study is: 2016-000584-16.