

Clinical Trial Results – Layperson Summary

A study of atezolizumab plus bevacizumab compared to sorafenib in people with liver cancer who have not had any chemotherapy

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 (May 2020).

The study started in March 2018 and is expected to end in June 2022. This summary includes the results that were collected and analysed in August 2019. At the time of writing this summary, the study is still going on – study doctors are still collecting information. This summary will be updated when the study ends.

One study can't tell us everything about the possible side effects of a medicine and how well it works. It takes lots of people in many studies to learn as much as we can about a medicine. This summary gives you information about the results from a study of a new treatment combination that may be an option within your treatment pathway. We have described the positive and negative results of this study in this summary, but all medical decisions regarding your individual case should be made by you and your doctor together, based on all the available information. **You should not make decisions based on this one summary. Always talk to your doctor before making any decisions about your treatment.**

Thank you to the people who took part in this study

The people who took part have helped researchers to answer important questions about liver cancer and about treatment with a medicine called atezolizumab (the study medicine) taken with another study medicine called bevacizumab.

Key information about this study

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?

- This study is being done to:
 - Compare treatment with atezolizumab plus bevacizumab versus treatment with sorafenib, to see which treatment works better in people with liver cancer that has spread to other parts of the body or cannot be cured with surgery (called ‘unresectable’ liver cancer).
 - Find out if atezolizumab plus bevacizumab could extend the life of people with unresectable liver cancer and give them a longer time before their cancer gets worse, compared to treatment with sorafenib.
 - Find out whether atezolizumab plus bevacizumab is safe in people with unresectable liver cancer (how many people had side effects and how severe they were).
- In this study, people are taking either the study medicine (a combination of atezolizumab plus bevacizumab – **Group A**) or an existing medicine (sorafenib – **Group B**).
- This study included 501 people in 17 countries/regions.
- So far, the study has shown that:
 - Two-thirds (67%) of the people in **Group A** were still alive 1 year after starting their treatment, compared to about half (55%) of the people in **Group B**.
 - In people in **Group A**, the tumours stopped growing for longer (an average of 7 months) than in people in **Group B** (whose tumours stopped growing for an average of 4 months).
 - More than one-quarter (27%) of the people in **Group A** saw their tumours get smaller, compared to just over one-tenth of people (12%) in **Group B**.
 - The quality of life of people in **Group A** took longer to get worse (an average of 11 months) than in people in **Group B**, whose quality of life got worse after an average of 4 months.
- About 38% of people (125 out of 329 people) in **Group A** had serious side effects, compared to about 31% of people (48 out of 126 people) in **Group B**.
- At the time of writing this summary, the study is still going on. It is expected to end in June 2022.

1. General information about this study

Why was this study done?

People with liver cancer that has spread to other parts of the body or is too large (or difficult) to remove with surgery usually take ‘targeted’ medicines. They are called targeted medicines because they can tell the difference between cancer cells and normal healthy cells and they ‘target’ and kill only the cancer cells. A targeted medicine called sorafenib is the ‘standard-of-care’ treatment for people with advanced liver cancer. However, targeted medicines do not work in everyone, or they only work for a short time and then the cancer gets worse again. Some people have to stop taking targeted medicines because the side effects make it too hard for them to keep on taking them.

Doctors can also choose to give a treatment called immunotherapy to people who have been previously treated with sorafenib. Immunotherapy is medicine that helps a person’s own immune system to attack

cancer cells. Immunotherapy medicines also work better in some people than in others, or work only for a short time. This may be because the cancer cells can ‘hide’ from the immune system and/or learn to ‘escape’ the immune system’s attacks.

Giving immunotherapy together with a different medicine acts like a ‘double attack’ on the cancer. This double attack may work better than either of the medicines on their own. Immunotherapy is sometimes combined with a type of medicine called an ‘anti-angiogenic’ treatment. Anti-angiogenic treatments stop the cancer cells from forming the new blood vessels that they need to grow and spread.

In this study, researchers wanted to see if combining an immunotherapy medicine with an anti-angiogenic treatment extended people’s lives and stopped their cancer from growing for longer than an existing targeted medicine. They also wanted to see whether the combination would be safe for people to take. These people’s liver cancer had not been treated with chemotherapy or targeted medicines before they started taking these medicines.

What medicines are being tested in the study?

This study looked at a study medicine called ‘atezolizumab’ (known by its brand name, Tecentriq®) taken together with another study medicine called bevacizumab (known by its brand name Avastin®) by the people in **Group A**.

- You say ‘atezolizumab’ 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.
- You say bevacizumab 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 that the cancer starves and can’t grow.
 - This is an ‘anti-angiogenic’ medicine.

To see whether the combination of atezolizumab plus bevacizumab would work better than the existing standard-of-care treatment for people with unresectable liver cancer, it was compared to the existing medicine sorafenib, taken by the people in **Group B**.

- You say this as ‘sor – a – fe – nib’.
- Sorafenib works by blocking the action of an abnormal protein that signals cancer cells to multiply. This helps stop the spread of cancer cells.
- Sorafenib is a type of targeted medicine.

What did researchers want to find out?

- Researchers wanted to see whether treating people who have unresectable liver cancer with a combination of medicines (atezolizumab plus bevacizumab) would extend their lives and/or the amount of time before their cancer got worse, compared to sorafenib.
 - See section 4 “What were the results of the study?”.

- They also wanted to find out how safe the combination of medicines is – by counting how many people had side effects (and seeing how severe these side effects were) when taking both medicines together during this study.
 - o See section 5 “What were the side effects?”.

The main questions that researchers wanted to answer were:

1. How long did people in **Group A** live in this study, compared to those in **Group B**?
2. How much time was there between the start of the treatment (atezolizumab plus bevacizumab in **Group A** or sorafenib in **Group B**) and the cancer getting worse?
3. How safe is the combination of atezolizumab plus bevacizumab? How many people in **Group A** and **Group B** had side effects and how severe were they?

Other questions that researchers wanted to answer included:

4. How many people in each group had smaller or no tumours after taking their medicine?
5. How much time was there before people in each group felt their quality of life got worse?

What kind of study was this?

This was a ‘Phase 3’ study. This means that atezolizumab plus bevacizumab had already been tested in a smaller number of people with liver cancer in a Phase 1b study called GO30140. Phase 3 studies are carried out in a large number of people to see if a drug works better than the standard treatment and is safe enough for it to be ‘approved’ by the authorities as a treatment that can be prescribed by your doctor.

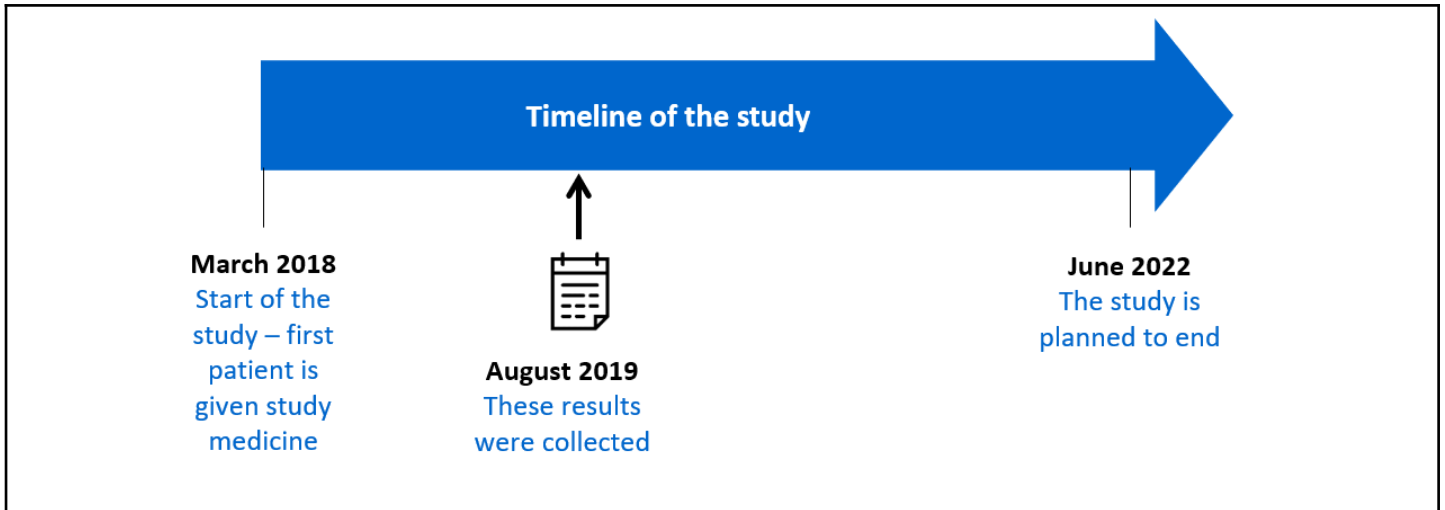
The study was ‘randomised’. This means that it was decided by a computer by chance to which treatment group, **A** or **B**, the people would be assigned – like tossing a coin.

- In this study, twice the number of people with liver cancer were in **Group A** (taking atezolizumab plus bevacizumab) than in **Group B** (taking sorafenib, the standard treatment for liver cancer).
- Randomly assigning the patients to either of the treatment groups makes it more likely that the characteristics of the people in both groups (eg., age, race, how sick they are) will be similar at the start of the study.

This was an ‘open label’ study. This means that both the people taking part in the study and the study doctors knew which medicines people were taking. Apart from the different medicines being tested in **Group A** and **Group B**, all other aspects of care were the same between the groups.

When and where did the study take place?

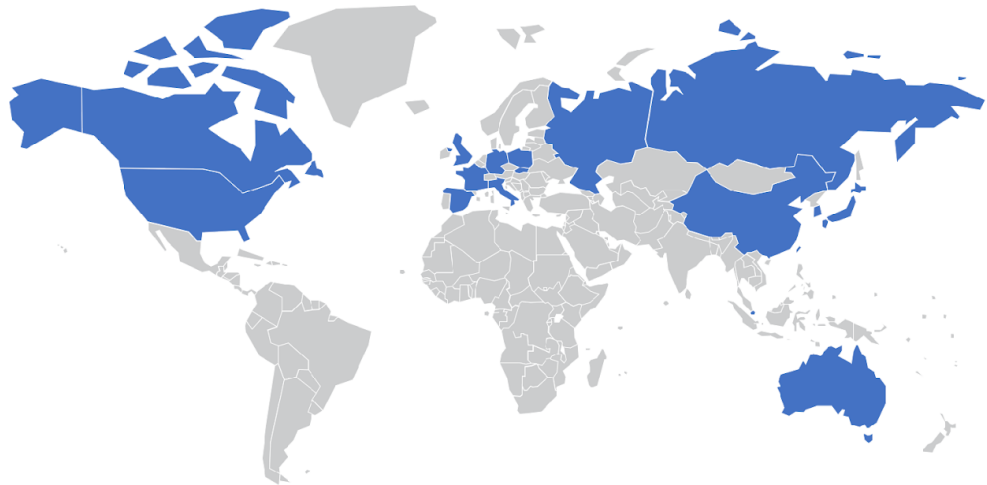
The study started in March 2018 and is expected to end in June 2022. This summary includes the results up until August 2019. At the time of writing this summary (May 2020), the study is still going on – study doctors are still collecting information.



This study is still going on. The symbol on the timeline (📅) shows when the information shown in this summary was collected – about 17 months after the start of the study.

The study took place at 111 study centres in 17 countries/regions around the world. The following map shows the countries/regions where this study took place.

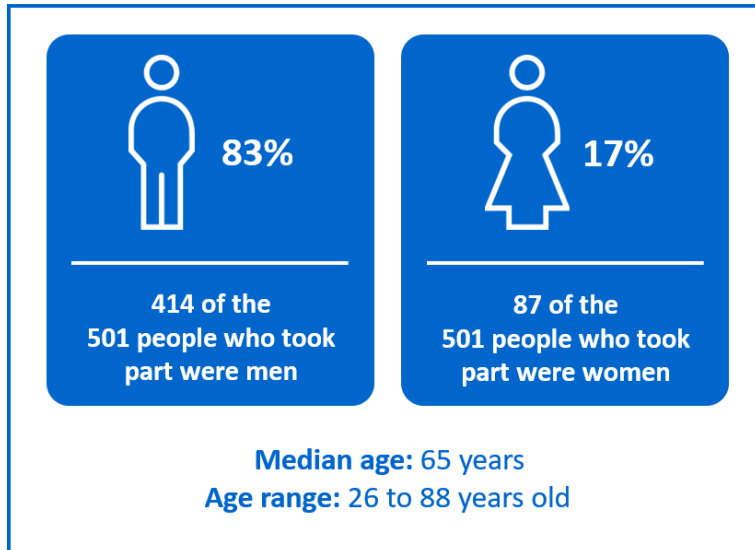
- Australia
- Canada
- China
- Czech Republic
- France
- Germany
- Hong Kong
- Italy
- Japan
- Korea
- Poland
- Russia
- Singapore
- Spain
- Taiwan
- UK
- USA



2. Who took part in this study?

In this study, 501 adults with liver cancer that had spread to other parts of the body and/or could not be cured with surgery took part. They had not taken chemotherapy or other medicine to treat their liver cancer before this study.

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



3. What happened during the study?

During the study, people were selected by chance to get one of two treatments. The treatments were selected at random by a computer.

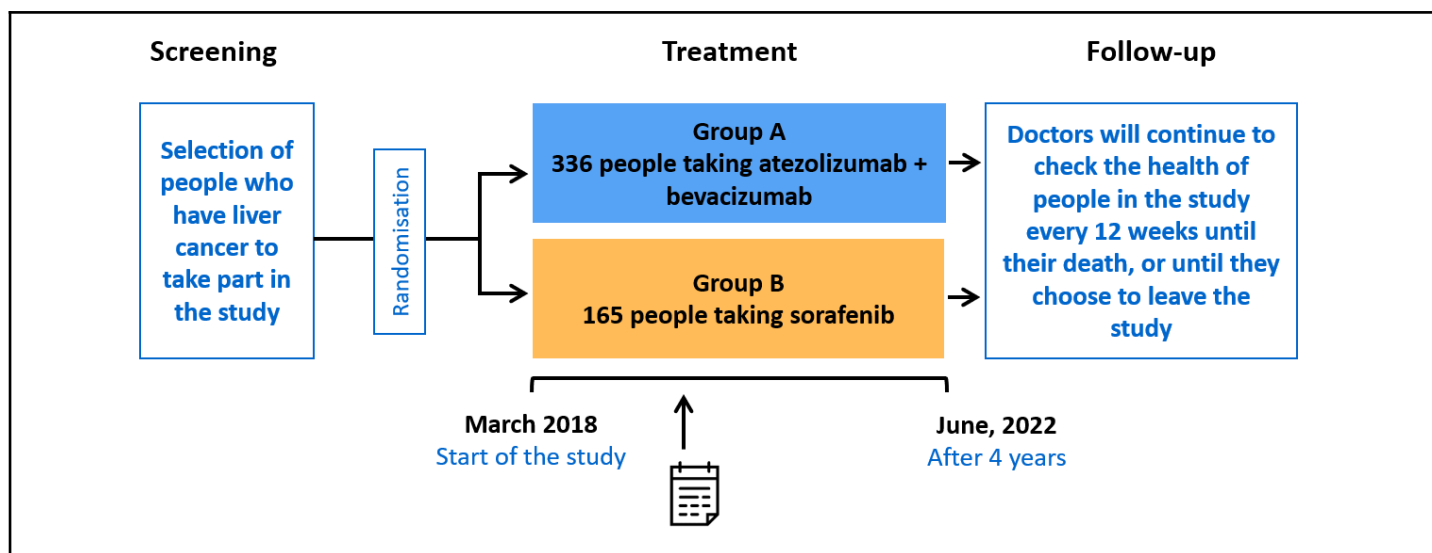
The treatments were:

- **Group A:** Atezolizumab plus bevacizumab (study medicine)
- **Group B:** Sorafenib (existing medicine).

This table shows the number of people who took each study treatment, and how often the drugs were taken.

	Group A Atezolizumab plus bevacizumab	Group B Sorafenib
Number of people taking this medicine	336	165
When and how the drugs were taken	Injected into a vein once every 3 weeks	Taken by mouth twice a day

Look below to see more information about what has happened in the study so far – and what the next steps are.



This study is still going on. The symbol on the timeline (📅) shows when the information shown in this summary was collected (August 2019 – around 17 months after the study started).

- Some people are still being treated with these medicines.
- When people on the study stop taking treatment, they will be asked to go back to their study centre for more visits to check their overall health. These people will continue to be checked until the study ends. These visits are important to determine how long people live on this study.

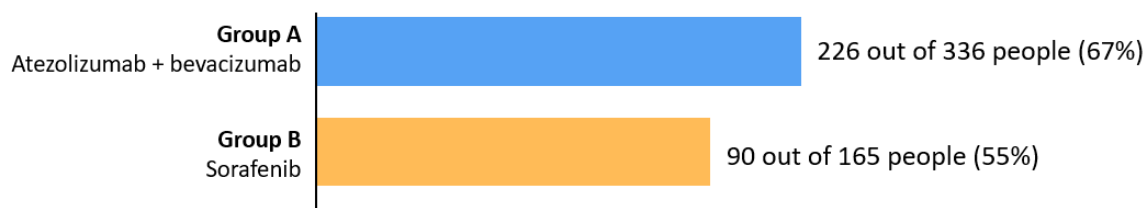
4. What were the results of the study at this point?

Question 1: How long did people in **Group A** live in this study, compared to those in **Group B**?

- When this information was collected and analysed in August 2019, 17 months after the study started:
 - 96 out of 336 patients in **Group A** (29% or nearly 3 out of 10) had died.
 - 65 out of 165 patients in **Group B** (39% or nearly 4 out of 10) had died.
- At the time this information was collected in August 2019, the average time that the people in **Group A** survived could not be calculated because not enough of these patients had died.
 - This study is still going on and the doctors will be able to calculate how long people in **Group A** live the next time they collect the study results.
 - The people in **Group B** (who were taking sorafenib) lived for an average of 13 months after they started taking their study treatment (some people lived longer and some people died sooner than 13 months).
 - This average survival time of 13 months may change as the study continues and people are followed up for longer.

A different way to see which treatment helps people with liver cancer to live longer is to compare how many people in each group were still alive 1 year after starting their treatment – this is shown below.

How many people were still alive 1 year after starting their treatment?



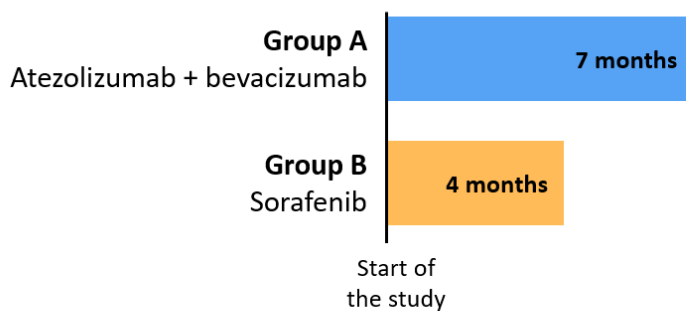
This information was collected from March 2018 until August 2019 and may change as the study continues.

- So far, the study showed that two-thirds of people (67%) in **Group A** were alive 1 year after they started taking atezolizumab plus bevacizumab, compared to around half (55%) of the people in **Group B**.
- These numbers may change as the study continues and people are followed up for longer.

Question 2: How much time was there between the start of treatment in each group and the cancer getting worse?

Researchers also compared how much time there was before the cancer became worse (in other words, spread, spread further, or grew larger as shown by their scans) in each group. This information was collected from all the people in both groups from March 2018 until August 2019.

On average, how much time was there between the start of treatment and the cancer getting worse?

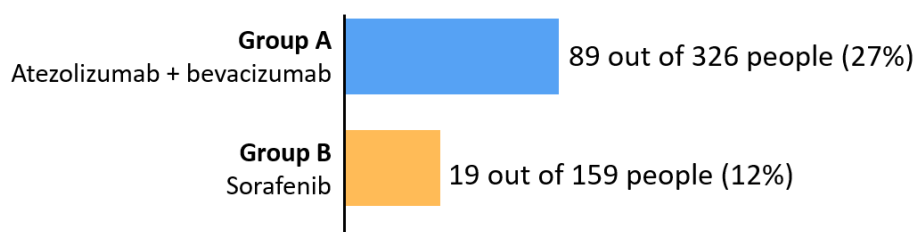


This information was collected from March 2018 until August 2019 and may change as the study continues.

- So far, the study showed that among all the people in **Group A**, the cancer became worse after an average of 7 months (some people's cancer took longer to get worse and some people's cancer got worse sooner than 7 months).
- In **Group B**, the cancer became worse after an average of 4 months (some people's cancer took longer to become worse and some people's cancer became worse sooner than 4 months).
- These average times may change as the study continues and people are followed up for longer.

Question 4. How many people in each group had smaller or no tumours after taking their medicine?

How many people had smaller tumours after taking their medicine?

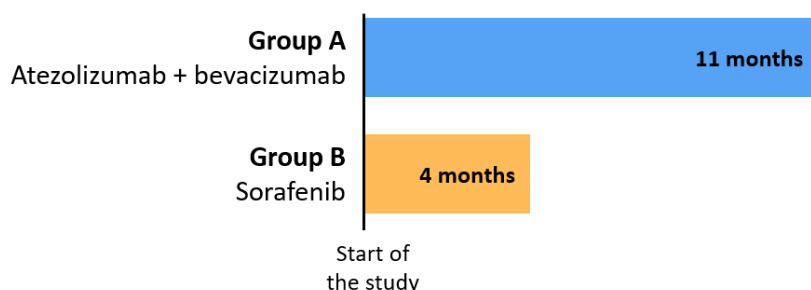


This information was collected from March 2018 until August 2019 and may change as the study continues.

- So far, more than one-quarter (27%) of the people in **Group A** had their tumours get smaller, compared to just over one-tenth of people (12%) in **Group B**.
- In **Group A**, 6 out of 100 people (6%) had their tumours shrink until they became too small to be measured using scans, compared to none of the people (0%) in **Group B**.
- These numbers may change as the study continues and people are followed up for longer.

Question 5. How much time was there before people in each group felt their quality of life got worse?

On average, how much time was there before people felt their quality of life got worse?



The people in this study filled out a questionnaire every 3 weeks that asked them about how they were feeling in their daily lives. Some of the questions asked if they felt weak, tired, depressed, in pain, or if they felt like vomiting. Other questions asked if they had trouble carrying out normal activities like eating, sleeping, concentrating, washing, using the toilet, going for walks, or doing their hobbies. Each answer scored points depending on how well they felt that week. The total points from the questionnaires each person filled out during the study showed researchers how their 'quality of life' was changing over time.

This information was collected from March 2018 until August 2019 and may change as the study continues.

- So far, the study showed that for people in **Group A**, their quality of life got worse after an average of 11 months (some people's quality of life took longer to get worse and some people's quality of life got worse sooner than 11 months).
- For people in **Group B**, their quality of life got worse after an average of 4 months (some people's quality of life took longer to get worse and some people's quality of life got worse sooner than 4 months).

- These average times may change as the study continues and people are followed up for longer.

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

5. What were the side effects?

Side effects (also known as ‘adverse reactions’) are medical problems (such as a vomiting) 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.

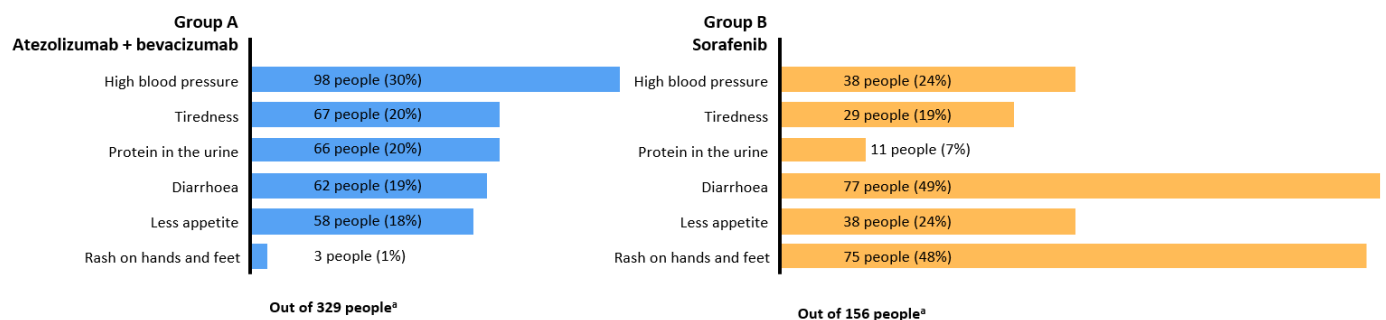
Common and serious side effects are listed in the following sections.

Most common side effects

The most common side effects are shown in the following picture – these are the side effects that happened in one-fifth (20%) or more of the people in either **Group A** or **Group B**.

- The side effects in this study were the same as side effects that have been experienced by other people who have taken atezolizumab and/or bevacizumab in other studies, or as prescribed by their doctors.
- The people taking atezolizumab plus bevacizumab in this study did not experience any new or unexpected side effects, compared to people in other studies of each individual medicine.

How many people had each of these side effects?



^a Some people left the study without taking any study medicines, and so they were not included in the total number

Side effects thought to be caused by medicines tested in the study

During this study, about 9 out of every 10 people (87%) had a side effect that their doctors thought was caused by the study medicines they were taking (called a ‘treatment-related’ side effect).

- In nearly half the people in both groups (47% of **Group A** and 48% in **Group B**) the treatment-related side effects were mild or moderately severe (classified as ‘grade 1 or 2’ severity – they caused mild symptoms [grade 1] or some limitations of activities [grade 2]).

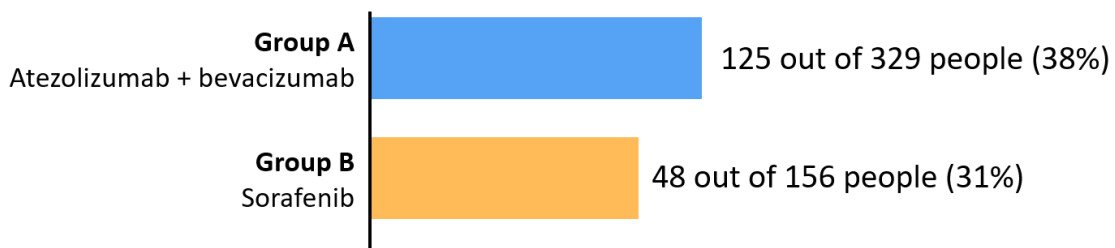
- Just over one-third of patients in **Group A** (36%) and nearly half the patients in **Group B** (46%) had a treatment-related adverse event that needed hospital care ('grade 3' severity) or was life-threatening ('grade 4' severity).

Serious side effects

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

- During this study, overall, just over one-third of people (36%) had at least one serious side effect.

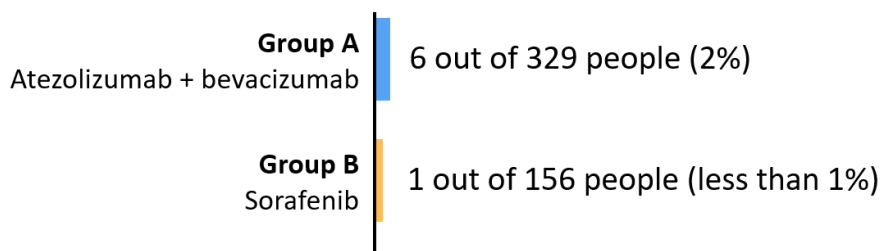
How many people had at least one serious side effect?



Some people in the study died because of side effects that may have been related to one of the treatments they were taking. These were:

- 6 out of 329 people (2%) in **Group A**.
- 1 out of 156 people (less than 1%) in **Group B**.

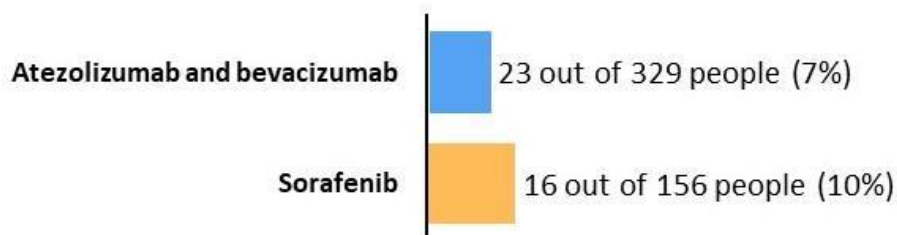
How many people died because of side effects?



Stopping the medicine because of side effects

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

How many people decided to stop taking their medicine because of side effects?



Other side effects

You can find information about other side effects (not shown in the sections above) in the medical journal article 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 501 people with liver cancer. The study is still going on, but researchers have been able to review the results so far. These results are helping researchers learn more about liver cancer and treatment with atezolizumab plus bevacizumab.

- So far, the study has shown that:
 - Two-thirds (67%) of the people in **Group A** were still alive 1 year after starting their treatment, compared to about half (55%) of those in **Group B**.
 - In **Group A**, people's tumours stopped growing for longer (an average of 7 months) than in people in **Group B** (whose tumours stopped growing for an average of 4 months).
 - More than one-quarter (27%) of the people in **Group A** had their tumours get smaller, compared to just over one-tenth of people (12%) in **Group B**.
 - The quality of life of people in **Group A** took longer to get worse (an average of 11 months) than in people in **Group B**, whose quality of life got worse after an average of 4 months.
 - The most common side effects in **Group A** were high blood pressure (in less than one-third of the people [30%]), tiredness (in one-fifth of the people [20%]) and protein in the urine (in one-fifth of the people [20%]).
 - The most common side effects in **Group B** were diarrhoea (in nearly half the people [49%], rashes on the hands and feet (in nearly half the people [48%]), high blood pressure (in nearly one-quarter of the people [24%]) and less appetite (in nearly one-quarter of the people [24%]).
 - More than one-third of the people in **Group A** (38%) had a serious side effect, compared to less than one-third of the people in **Group B** (31%).
 - In **Group A**, 6 out of 329 people (2%) and in **Group B**, 1 out of 156 people (less than 1%) died because of side effects that may have been related to one of the treatments they were taking.

This summary gives you information about the results from a large phase 3 study of a new treatment combination. However, one study can't tell us everything about how safe a medicine is and how well it works. We have described all the positive and negative results of this study in this summary, but all medical decisions regarding your individual case should be made by you and your doctor together, based on all the available information.

- 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?

Another trial (IMbrave050; NCT04102098) is happening now in people who have liver cancer that has not spread outside of the liver, and who have had surgery with the aim of curing their cancer. In IMbrave050, these people will either receive atezolizumab plus bevacizumab, or be closely watched by their doctors to see if their cancer returns.

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/NCT03434379>
- <https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-003691-31/GB>
- <https://forpatients.roche.com/en/trials/cancer/hepatocellular-carcinoma/a-study-of-atezolizumab-in-combination-with-bevacizumab-compared.html>

If you would like to find out more about the results of this study, the full title of the scientific paper that describes this study is: "Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma". The authors of the scientific paper are: Richard S. Finn, Shukui Qin, Masafumi Ikeda, and others. The paper is published in the journal '*New England Journal of Medicine*', volume number 382, on pages 1894-1905.

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/hepatocellular-carcinoma/a-study-of-atezolizumab-in-combination-with-bevacizumab-compared.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 Study of Atezolizumab in Combination With Bevacizumab Compared With Sorafenib in Patients With Untreated Locally Advanced or Metastatic Hepatocellular Carcinoma (IMbrave150)".

- The protocol number for this study is: YO40245.

- The ClinicalTrials.gov identifier for this study is: NCT03434379.
- The EudraCT number for this study is: 2017-003691-31.