Summary of Clinical Trial Results

MORPHEUS-Colorectal Cancer Study: data from subgroups of previously treated people who received atezolizumab with idasanutlin, atezolizumab with LOAd703, atezolizumab with etrumadenant and regorafenib, or atezolizumab with regorafenib compared to people who were treated with regorafenib alone

See the end of the summary for the full title of the study.

About This Summary

This is a summary of the results from 5 small groups of people (each group is called a 'subgroup' in this document) who were part of a large clinical trial (called a 'study' in this document) known as the MORPHEUS-Colorectal Cancer Study.

This summary has been written for people who took part in the MORPHEUS-Colorectal Cancer Study and members of the public.

This summary is based on information known at the time that this summary was written in September 2023. The MORPHEUS-Colorectal Cancer Study has been completed.

Key Questions

Thank you to our study participants!

Clinical study participants belong to a large community of people around the world who have made it possible for researchers to answer important health questions and discover new medicines. Thank you!

The people who took part in this study were included in 1 of 5 subgroups: 1) the "**Idasanutlin Group**" started in February 2020 and finished in November 2021, 2) the "**LOAd703 Group**" started in May 2022 and finished in August 2022, 3) the "**Etrumadenant Group**" started in July 2020 and finished in January 2022, 4) the "**Regorafenib Group**" started in July 2020 and finished in September 2022, and 5) the "**Control Group**," treated with **regorafenib alone**, started in October 2018 and

finished in February 2022. The 60 participants in these subgroups helped researchers find out how safe atezolizumab is and how well it works when used in combination with **idasanutlin**, **LOAd703**, **etrumadenant and regorafenib**, or **regorafenib** compared to treatment with **regorafenib alone** for people with colorectal cancer.

As the company that organized and funded this study (sponsor), Roche would like to share the results with everyone. It is important to remember that one study can't tell us everything about the possible side effects of a drug and how well it may work. It takes a lot of people in many studies to learn as much as we can about combinations of medicines like **atezolizumab with idasanutlin**, **atezolizumab with LOAd703**, **atezolizumab with etrumadenant and regorafenib**, and **atezolizumab with regorafenib**. The results of this study may be different from the results of other studies with these medicines. **This means that you should not make medical decisions based on this one summary. Always talk with your doctor before making any decisions about your treatment.**

1. What has happened since these subgroups ended?

The larger MORPHEUS-Colorectal Cancer study and the subgroups described here have been completed.

The **Idasanutlin Group**, which looked at a subgroup of 4 people who were given **atezolizumab plus idasanutlin**, took 21 months (almost 2 years) to complete and included people from 3 countries.

The **LOAd703 Group**, which looked at a subgroup of 2 people who were given **atezolizumab plus LOAd703**, took 3 months to complete and included people from 1 country (United States).

The **Etrumadenant Group**, which looked at a subgroup of 15 people who were given **atezolizumab plus etrumadenant and regorafenib**, took 18 months (1.5 years) to complete and included people from 3 countries.

The **Regorafenib Group**, which looked at a subgroup of 15 people who were given **atezolizumab plus regorafenib**, took 26 months (over 2 years) to complete and included people from 4 countries.

The **Control Group**, which looked at a subgroup of 19 people who were given **regorafenib alone**, took 40 months (over 3 years) to complete and included people from 5 countries.

2. Why was this research needed?

Current treatments for colorectal cancer include chemotherapy, which kills cancer cells and stops the cancer from growing. People with colorectal cancer take a combination of different chemotherapies to treat their cancer. However, these medicines may work for only a short time and then the cancer gets worse again. Also, in some people, the cancer still grows even with treatment.

Therefore, new medicines are needed to treat this type of cancer and shrink the tumour. If the tumour shrinks, a person may start to feel better and may have a better quality of life.

One type of medicine that has helped people with cancer live longer is cancer 'immunotherapy,' which helps one's own immune system to find and fight cancer. Normally, cancer cells block (stop) the immune system from attacking cancer, which lets the tumours become larger. Cancer immunotherapies, like atezolizumab, release this blockage and help the immune system fight cancer. Researchers think that cancer immunotherapies might work better to shrink tumours if they are combined with other medicines.

Specifically, researchers wanted to know if treating people who have colorectal cancer with atezolizumab in combination with other medicines would help them live longer and/or lengthen the amount of time before their cancer got worse, compared to people who were treated with a standard medicine, **regorafenib alone**. The other medicines to be combined with atezolizumab include: **idasanutlin**, **LOAd703**, **etrumadenant plus regorafenib**, and **regorafenib**.

Researchers also wanted to find out how safe these combinations of medicines are by counting the number of people who had side effects and seeing how severe these side effects were.

The results for these subgroups of people helped answer the following important questions:

- How many people had smaller or no tumours after taking their medicine?
- How many people had side effects, and how severe were these side effects?

3. General information about these subgroups

The MORPHEUS-Colorectal Cancer Study was made up of many subgroups. Of these subgroups, 5 are summarised here. Each subgroup included people who received one of the following combinations of medicines: **atezolizumab with idasanutlin**, **atezolizumab with LOAd703**, **atezolizumab with etrumadenant and regorafenib**, **atezolizumab with regorafenib**, or the standard medicine, **regorafenib alone**.

The MORPHEUS-Colorectal Cancer Study also included people at different stages of their treatment. For example, when people get their first treatment, this is known as 'first-line' treatment. For people who already received a treatment and had their disease get worse, their next treatment is called 'second-line'. For people who received 2 different types of treatments and still had their disease get worse, their next treatment is called 'third-line'. In the MORPHEUS-Colorectal Cancer Study, people received second-line or third-line treatment. People in this study were put into different study subgroups by chance and received different combinations of medicines depending on which subgroup they were in.

What medicines were used to treat people in these subgroups?

For the subgroups described in this summary, people with colorectal cancer whose cancer got worse after first-line or second-line standard medicines were split into 5 smaller groups: the **Idasanutlin Group**, the **LOAd703 Group**, the **Etrumadenant Group,** the **Regorafenib Group,** and the **Control Group**.

The first 4 subgroups looked at a medicine called 'atezolizumab' (known by its brand name, TECENTRIQ®) taken together with additional medicines.

- **Atezolizumab** (you say this as 'a – teh – zo – liz – oo – mab')
    - This medicine is a type of immunotherapy.
    - The body's immune system fights diseases like cancer. But cancer cells can block (stop) the immune system from attacking the cancer. Atezolizumab releases this blockage – meaning that the immune system again becomes able to fight the cancer cells.

People in the **Idasanutlin Group** were treated with **atezolizumab** taken together with a medicine called **idasanutlin**.

- **Idasanutlin** (you say this as 'i – DAH – sah – nut- lin')

- This medicine is an 'MDM2 inhibitor'.
- Cancer cells can switch off an important protein called p53. This protein would normally send a signal to the body to kill the cancer cell. When the protein is switched off, the cancer cells continue to multiply. **Idasanutlin** switches this protein back on, which means the cancer cells will stop growing and die.

People in the **LOAd703 Group** were treated with **atezolizumab** taken together with a medicine called **LOAd703**.

- **LOAd703** (you say this as 'loh – ad – 7 – 0 - 3')
  - This medicine is a type of virus that works in 2 ways:
    - The LOAd703 virus enters (infects) cancer cells and can kill them directly.
    - LOAd703 can also infect other cells surrounding the cancer cells to make them produce proteins which help the immune system find and attack the cancer cells.

People in the **Etrumadenant Group** were treated with **atezolizumab** taken together with medicines called **etrumadenant** and **regorafenib**. Regorafenib is a medicine that has already been approved for use alone (known by its brand name, STIVARGA®).

- **Etrumadenant** (you say this as 'eh – tru – MA – de - nant')
  - This medicine is designed to block (stop) 'adenosine' activity.
  - Cancer cells produce a substance called adenosine in excess. Too much adenosine can stop the body's immune system from killing cancer cells. **Etrumadenant** blocks the effects of adenosine, meaning that the immune system can work properly and kill cancer cells.
- **Regorafenib** (you say this as 're – goe – RAF – e - nib')
  - This medicine is known as a multikinase inhibitor.
  - Cancers grow larger by dividing into new cells, and they use certain proteins (also known as 'kinases') to help them do this. Regorafenib can block these proteins, preventing the signals that tell cancer cells to grow. Regorafenib may also stop the growth of blood vessels, so that the cancer cells starve and can't grow.

People in the **Regorafenib Group** were treated with **atezolizumab** taken together with **regorafenib**.

People in the **Control Group** were treated with **regorafenib alone**.

Please refer to Section 5 below for more details on each of these medicines.

What kind of study was this?

These 5 subgroups were part of a larger study called the MORPHEUS-Colorectal Cancer Study. MORPHEUS was a 'Phase 1b/2' study (also known as an early research study) that looks at how well a new combination of cancer medicines works and how safe the medicines are. Each subgroup contained a small number of people who took 1 of 5 different combinations of medicines or a standard medicine (control), and researchers did medical tests on these people to find out if taking a combination of medicines had any effect on treating their cancer.

The people in these subgroups were 'randomised,' meaning that they were randomly put into 1 of 5 smaller groups – **Idasanutlin**, **LOAd703**, **Etrumadenant**, **Regorafenib**, or **Control** – by chance. Randomly putting people into groups makes it more likely that the characteristics of the people in all groups (for example, age, race, and how sick they are) will be similar at the start of the study.

This part of the study used an 'open label' design, which means that both the study researchers and the people in these subgroups knew which medicines people were taking. Apart from the different medicines being tested in the **Idasanutlin**, **LOAd703**, **Etrumadenant**, **Regorafenib**, and **Control Groups**, all other aspects of care were the same between the 5 subgroups.

When and where did the study of these subgroups take place?

These 5 subgroups were part of a larger study called the MORPHEUS-Colorectal Cancer Study. This study has now ended. This summary includes the results up to September 2022.

The study took place at 15 study centres in 5 countries (Australia, France, South Korea, Switzerland, and the United States).

4. Who was part of these subgroups?

The 5 subgroups enrolled a total of 60 people with colorectal cancer: 48% were men and 52% were women. They were 34 to 75 years old. Of these 60 people, 55 received treatment and were included in the analysis of the medicines. Each person had cancer that had spread to other parts of the body and had already been given treatments that had not worked or had stopped working.

5. What medicines were given to people in these subgroups?

People were randomly placed into the **Idasanutlin Group**, **LOAd703 Group**, **Etrumadenant Group**, **Regorafenib Group**, or **Control Group** by a computer and were given specific treatments. The tables below show what medicines were used to treat people in each subgroup, and when and how the medicines were taken.

Idasanutlin Group		
	Atezolizumab	**Idasanutlin**
Number of people taking this medicine	4	
When and how the medicines were taken	Injected into a vein on Days 1 and 15 of every 28-day cycle	Given by mouth on Days 1-5 of every 28-day cycle
How long treatment was expected to last	Until their disease got worse or treatment was stopped for safety reasons	
Target end date of treatment	No target end date. People received treatment until their disease got worse	

LOAd703 Group		
	Atezolizumab	**LOAd703**
Number of people taking this medicine	2	
When and how the medicines were taken	Injected into a vein on Day 1 of every 21-day cycle	Injected into the tumour on Day 1 of every 21-day cycle
How long treatment was expected to last	Until their disease got worse or treatment was stopped for safety reasons	
Target end date of treatment	No target end date. People received treatment until their disease got worse	

Etrumadenant Group			
	Atezolizumab	**Regorafenib**	**Etrumadenant**
Number of people taking this medicine	15		
When and how the medicines were taken	Injected into a vein on Days 1 and 15 of every 28-day cycle	Given by mouth on Days 1-21 of every 28-day cycle	Given by mouth on Days 1-28 of every 28-day cycle
How long treatment was expected to last	Until their disease got worse or treatment was stopped for safety reasons		
Target end date of treatment	No target end date. People received treatment until their disease got worse		

Regorafenib Group		
	Atezolizumab	**Regorafenib**
Number of people taking this medicine	15	
When and how the medicines were taken	Injected into a vein on Days 1 and 15 of every 28-day cycle	Given by mouth on Days 1-21 of every 28-day cycle
How long treatment was expected to last	Until their disease got worse or treatment was stopped for safety reasons	
Target end date of treatment	No target end date. People received treatment until their disease got worse	

Control Group	
	Regorafenib
Number of people taking this medicine	19
When and how the medicines were taken	Given by mouth on Days 1-21 of every 28-day cycle
How long treatment was expected to last	Until their disease got worse or treatment was stopped for safety reasons
Target end date of treatment	No target end date. People received treatment until their disease got worse

6. What were the results for these subgroups?

After treatment, researchers found that:

- Of the 25 people collectively in the **Idasanutlin Group**, **LOAd703 Group**, or **Control Group**, no one had their tumours shrink as a result of their treatment.
- Of the 15 people in the **Etrumadenant Group**, 1 person (7%) had their tumour shrink as a result of their treatment.
- Of the 15 people in the **Regorafenib Group**, 1 person (7%) had their tumour shrink as a result of their treatment.

7. What side effects did people in these subgroups experience?

Side effects are unwanted medical problems (such as fever or headache) that happen during the study.

- They are described in the summary because the study researchers believe that these side effects may be related to the treatments in the study.
- Not all of the people in these subgroups had all the side effects listed below.
- Side effects may be mild to very serious and can be different from person to person.

It is important to know that the side effects reported in this summary are from the people involved in these subgroups only. This means that the side effects listed here may be different from those seen in other people, other groups, and/or other studies of the same medicines. The side effects listed here may also be different than what is included in the patient leaflets, brochures, or websites for any of the medicines that were used in this study. However, researchers did not see any new or unusual side effects in this study different from those that have already been found in other studies of the medicines that were used.

Information about common and serious side effects seen in these subgroups are listed below.

Top 5 or more most common side effects

Here are the most common side effects seen in the 4 patients treated in the Idasanutlin Group (seen in at least 2 out of 4 people [50%]):

- Feeling sick: 4 out of 4 people (100%)
- Throwing up: 4 out of 4 people (100%)
- Diarrhoea: 2 out of 4 people (50%)
- Low level of the blood cell fragments that help blood to clot – called 'platelets': 2 out of 4 people (50%)
- Liver, heart, or kidney damage – shown by higher levels of something called 'AST' in the blood: 2 out of 4 people (50%)
- Increased levels of bilirubin in the blood: 2 out of 4 people (50%)

Here are the most common side effects seen in the 2 patients treated in the LOAd703 Group (seen in at least 1 out of 2 people [50%]):

- Feeling tired: 2 out of 2 people (100%)
- Poor appetite: 1 out of 2 people (50%)
- Feeling sick: 1 out of 2 people (50%)
- Pain in the stomach area: 1 out of 2 people (50%)
- Swelling of the stomach area: 1 out of 2 people (50%)
- Condition causing fever, vomiting, shortness of breath, headache and low blood pressure: 1 out of 2 people (50%)
- Being short of breath: 1 out of 2 people (50%)
- Rash with flat and raised parts of the skin: 1 out of 2 people (50%)

Here are the most common side effects seen in the 15 patients treated in the Etrumadenant Group (seen in at least 4 of 15 people [27%]):

- Fever: 9 out of 15 people (60%)
- Rash with flat and raised parts of the skin: 6 out of 15 people (40%)
- Poor appetite: 5 out of 15 people (33%)
- Pain in the stomach area: 4 out of 15 people (27%)
- Diarrhoea: 4 out of 15 people (27%)
- Feeling tired: 4 out of 15 people (27%)
- Reaction to injection into a vein: 4 out of 15 people (27%)
- Hand-foot syndrome: 4 out of 15 people (27%)
- Inflammation or irritation of the mouth: 4 out of 15 people (27%)

Here are the most common side effects seen in the 15 patients treated in the Regorafenib Group (seen in at least 4 out of 15 people [27%]):

- Diarrhoea: 7 out of 15 people (47%)
- Feeling tired: 7 out of 15 people (47%)
- Poor appetite: 6 out of 15 people (40%)
- Low energy levels: 5 out of 15 people (33%)
- Hand-foot syndrome: 5 out of 15 people (33%)
- Fever: 5 out of 15 people (33%)
- Pain in the muscles: 4 out of 15 people (27%)

Here are the most common side effects seen in the 19 patients treated in the Control Group (seen in at least 5 of 19 people [26%]):

- Hand-foot syndrome: 12 out of 19 people (63%)
- Feeling tired: 8 out of 19 people (42%)
- Feeling sick: 7 out of 19 people (37%)
- Poor appetite: 6 out of 19 people (32%)
- Diarrhoea: 6 out of 19 people (32%)
- High blood pressure: 6 out of 19 people (32%)
- Pain in the stomach area: 5 out of 19 people (26%)
- Increased levels of bilirubin in the blood: 5 out of 19 people (26%)
- Trouble with speaking: 5 out of 19 people (26%)
- Pain in the arms and legs: 5 out of 19 people (26%)

People taking the medicine combinations in this study (in any of the subgroups) did not experience any new or unexpected side effects compared to people in other studies of each individual medicine.

Some side effects were thought to be caused by the drugs tested in the 4 subgroups

During this study, 52 out of 55 people (95%) had a side effect that the researchers thought was caused by the study medicines they were taking. This is called a 'treatment-related' side effect.

A treatment-related side effect happened in:

- 4 out of 4 people (100%) in the Idasanutlin Group
- 1 out of 2 people (50%) in the LOAd703 Group
- 15 out of 15 people (100%) in the Etrumadenant Group
- 14 out of 15 people (93%) in the Regorafenib Group
- 18 out of 19 people (95%) in the Control Group

Serious side effects

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

The serious side effects that the researchers thought were caused by the study medicines are shown below. Some people had more than 1 side effect – this means that they are included in more than 1 row in the table.

During this study, a treatment-related serious side effect happened in:

- 1 out of 4 people (25%) in the **Idasanutlin Group**
- 1 out of 2 people (50%) in the **LOAd703 Group**
- 5 out of 15 people (33%) in the **Etrumadenant Group**
- 4 out of 15 people (27%) in the **Regorafenib Group**
- 1 out of 19 people (5%) in the **Control Group**

Treatment-related serious side effects reported in this group	People in the Idasanutlin Group (4 people)
Low level of the blood cell fragments that help blood to clot – called 'platelets'	25% (1 out of 4)

Treatment-related serious side effects reported in this group	People in the LOAd703 Group (2 people)
Condition causing fever, vomiting, shortness of breath, headache and low blood pressure	50% (1 out of 2)

Treatment-related serious side effects reported in this group	People in the Etrumadenant Group (15 people)
Low level of white blood cells, with fever	7% (1 out of 15)
Rash with flat and raised parts of the skin	7% (1 out of 15)
Allergic reactions	7% (1 out of 15)
Fever	7% (1 out of 15)
Low energy levels	7% (1 out of 15)
Rash	7% (1 out of 15)

- People in the **Etrumadenant Group** could have had more than 1 treatment-related serious side effect.

Treatment-related serious side effects reported in this group	People in the Regorafenib Group (15 people)
Fever	13% (2 out of 15)

Feeling sick	7% (1 out of 15)
Kidney infection	7% (1 out of 15)
Clotting inside tiny blood vessels leading to low levels of blood cells	7% (1 out of 15)
Rash with flat and raised parts of the skin	7% (1 out of 15)

- People in the **Regorafenib Group** could have had more than 1 treatment-related serious side effect.

Treatment-related serious side effects reported in this group	**People in the Control Group (19 people)**
High levels of white blood cells	5% (1 out of 19)
Tunnel-like hole inside the body between two organs or blood vessels	5% (1 out of 19)

Side effects that caused death

One person in the study died due to side effects that may or may not have been related to one of the study medicines.

- There were no fatal side effects in the **Idasanutlin**, **LOAd703**, or **Etrumadenant Groups**.
- One person in the **Regorafenib Group** (7%) died because of bleeding in the tumour, which the researchers thought was not related to the study medicines.
- Two people in the **Control Group** (11%) died because of a serious side effect of a reaction to an infection sometimes called blood poisoning ('sepsis'), which the researchers thought was not related to the study medicines.

Stopping the medicine because of side effects

During the study, some people decided to stop taking their medicine because of side effects that were related to one of the study medicines.

- In the **Idasanutlin** and **LOAd703 Groups**, no patients stopped taking their medicine because of a related side effect.
- In the **Etrumadenant Group**, 1 person (7%) stopped taking their medicine because of a related side effect.
- In the **Regorafenib Group**, 1 person (7%) stopped taking their medicine because of a related side effect.
- In the **Control Group**, 2 people (11%) stopped taking their medicine because of a related side effect.

8. What do these results mean for patients and researchers?

The information in this summary is from part of the larger MORPHEUS-Colorectal Cancer Study. These results are for the subgroups of patients who were given 1 of 4 combinations of medicines:

atezolizumab with idasanutlin, **atezolizumab with LOAd703**, **atezolizumab with etrumadenant and regorafenib**, **atezolizumab with regorafenib**, or the control medicine **regorafenib**. These results have helped researchers learn more about how atezolizumab interacts with other medicines for the treatment of people with colorectal cancer.

It is important to remember that **one study cannot tell us everything we need to know about how safe a medicine is and how well it works**. It takes a lot of people in many studies to truly understand everything we need to know. The results of these studies may be different from results of other studies of the same medicines. **This means that you should not make medical decisions based on this one summary. Always speak with your doctor before making any decisions about your treatment.**

9. Are there plans to do other studies with these medicines?

Currently no other studies are looking at the use of atezolizumab together with **idasanutlin**, **LOAd703**, **etrumadenant and regorafenib**, or **regorafenib** for the treatment of colorectal cancer.

10. Where can I find more information?

You can find more information about this study on the following websites:

- https://clinicaltrials.gov/ct2/show/NCT03555149
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-004566-99
- https://forpatients.roche.com/en/trials/cancer/crc/a-study-evaluating-the-efficacy-and-safety-of-multiple-immunothe.html

Who can I contact if I have questions about these subgroups or the larger MORPHEUS-Colorectal Cancer Study?

If you have more questions, visit the link below and fill out the contact form.
https://forpatients.roche.com/en/trials/cancer/crc/a-study-evaluating-the-efficacy-and-safety-of-multiple-immunothe.html

Who organised and paid for these subgroups and the larger MORPHEUS-Colorectal Cancer Study?

The MORPHEUS-Colorectal Cancer Study and these subgroups were organised and paid for by F. Hoffmann-La Roche Ltd whose headquarters are in Basel, Switzerland. The **LOAd703 Group** was co-funded by Lokon Pharma (Uppsala, Sweden), and the **Etrumadenant** and **Regorafenib Groups** were co-funded by Arcus Biosciences (Hayward, California, United States). The medicine regorafenib was provided by F. Hoffmann-La Roche or purchased by study sites.

Full title of the study and other identifying information

The full title of the study is: “A Study of Multiple Immunotherapy-Based Treatment Combinations in Participants With Metastatic Colorectal Cancer (Morpheus-Colorectal Cancer)”

The study is also known as MORPHEUS-CRC.

- The protocol number for this study is: CO39612.
- The ClinicalTrials.gov identifier for this study is: NCT03555149.
- The EudraCT number for this study is: 2017-004566-99.