# Summary of Clinical Trial Results

## MORPHEUS-Colorectal Cancer Study: data from three subgroups of previously treated people who received atezolizumab with Imprime PGG plus bevacizumab or atezolizumab with isatuximab or atezolizumab with selicrelumab plus bevacizumab compared to those who were treated with regorafenib

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

## About This Summary

This is a summary of the results from four 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) called the MORPHEUS-Colorectal Cancer Study.

This summary has been written for people who are taking 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 January 2021.

The larger MORPHEUS study is still ongoing. This summary includes the results for four subgroups.

### Key Questions

1. What has happened since these subgroups ended?
2. Why was this research needed?
3. General information about these subgroups
4. Who was part of these subgroups?
5. What medicines were given to people in these subgroups?
6. What were the results for these subgroups?
7. What side effects did people in these subgroups experience?
8. What do these results mean for patients and researchers?
9. Are there plans to add other people to these subgroups or to do other studies with these medicines?
10. Where can I find more information?

## *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 in this study were part of one of four subgroups: 1) the "**Imprime Group**" started in September 2018 and finished in August 2020, 2) the "**Isatuximab Group**" started in September 2018 and finished in March 2020, 3) the "**Selicrelumab Group**" started in March 2019 and finished in March 2020, and 4) the "**Control Group**" with **regorafenib** started in September 2018 and this subgroup is still happening – study doctors are still collecting information. The 49 patients in this

study helped researchers find out how safe atezolizumab is and how well it works when used in combination with **Imprime PGG plus bevacizumab**, **isatuximab**, or **selicrelumab plus bevacizumab** compared to **regorafenib** for people with colorectal cancer.

As the company that organized and funded this study (sponsor), Roche would like to provide everyone the results of these studies. 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 Imprime PGG plus bevacizumab**, **atezolizumab with isatuximab**, or **atezolizumab with selicrelumab plus bevacizumab**. The results of these studies may be different from the results of other studies of 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 study and the **Control Group** are still ongoing. However, the combination subgroups described here have been completed.

The **Imprime Group**, which looked at a subgroup of 15 people who were given **atezolizumab plus Imprime PGG plus bevacizumab**, took 33 months (over 2 years) to complete and included people from 4 countries.

The **Isatuximab Group**, which looked at a subgroup of 15 people who were given **atezolizumab plus isatuximab**, took 33 months (over 2 years) to complete and included people from 4 countries.

The **Selicrelumab Group**, which looked at a subgroup of 6 people who were given **atezolizumab plus selicrelumab plus bevacizumab**, took 12 months (1 year) to complete and included people from 2 countries.

The **Control Group** is ongoing. Here we report on 13 people who were given **regorafenib**, reporting data collected until June 2021 and including 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 only **regorafenib**, a standard medicine. The other medicines to be combined with atezolizumab include

medicines that also activate the body's immune system to kill cancer cells (called 'Imprime PGG' or 'isatuximab' or 'selicrelumab') and a medicine that prevents cancer cells from growing their own blood vessels (called 'bevacizumab').

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 is made up of many subgroups. Of these subgroups, 4 are summarised here. Each subgroup includes people who received one of the following combinations of medicines: **atezolizumab with Imprime PGG plus bevacizumab**, **atezolizumab with isatuximab**, or **atezolizumab with selicrelumab plus bevacizumab**, or the standard medicine **regorafenib**.

The MORPHEUS-Colorectal Cancer Study also includes people at different stages of their treatments. For example, people getting their first treatment are receiving 'first-line' treatment. For people who received a treatment and had their disease get worse, their next treatment is called 'second-line'. For people who have 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. Further, people 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 in this summary, people with colorectal cancer whose cancer got worse after first-line or second-line standard medicines were split into four smaller groups – the **Imprime Group**, **Isatuximab Group**, **Selicrelumab Group,** and the **Control Group**.

The first three 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.
    - When people take atezolizumab, their tumour (cancer) may get smaller.

People in the **Imprime Group** were treated with **atezolizumab** taken together with medicines called **Imprime PGG and bevacizumab** (known by its brand name, AVASTIN®).

- **Imprime PGG** (you say this as 'im – PRIME – pee – gee – gee')
    - This medicine is an innate immune activator.

- The body's innate immune system provides the initial response to fighting disease, while the body's adaptive immune system requires more time to respond and generate longer-lasting protection against diseases such as cancer. Imprime PGG activates the innate immune system and also makes the adaptive immune system more able to respond to and destroy cancer cells.

- **Bevacizumab** (you say this as 'beh – vuh – SI – zuh – mab')
  - This medicine is an anti-angiogenic medicine.
  - 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.

The combination of Imprime PGG and bevacizumab may help atezolizumab work better so people's tumours (cancer) may get smaller.

People in the **Isatuximab Group** were treated with **atezolizumab** taken together with a medicine called **isatuximab** (known by its brand name, SARCLISA®).

- **Isatuximab** (you say this as 'i – suh - TUK - sih - mab')
  - This medicine is a type of immunotherapy.
  - The immune system is made up of many different types of cells that work together to protect the body from disease. Isatuximab binds to a protein used by some of these types of cells, which helps the immune system to kill the cancer.
    Isatuximab might help atezolizumab work better so people's tumours (cancer) may get smaller.

People in the **Selicrelumab Group** were treated with **atezolizumab** taken together with medicines called **selicrelumab and bevacizumab**.

- **Selicrelumab** (you say this as 'sel – ee - KREL - yoo - mab')
  - This medicine is a type of immunotherapy.
  - To attack a tumour, killer T cells of the immune system must be activated. Selicrelumab helps these cells become activated so that they can fight the cancer cells and destroy the tumour.
  - The combination of selicrelumab and bevacizumab with atezolizumab may boost the immune system to better eliminate the cancer.

People in the **Control Group** were treated with a medicine that has already been approved for use called **regorafenib** (known by its brand name, STIVARGA®).

- **Regorafenib** (you say this as 're – goe – RAF – e - nib')
  - This medicine is a multikinase inhibitor.
  - Cancers grow larger by dividing into new cells, and they use certain proteins 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.

### What kind of study was this?

These four subgroups are part of a larger study called the MORPHEUS-Colorectal Cancer Study. MORPHEUS is 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 one of three 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 one of four smaller groups – **Imprime**, or **Isatuximab**, or **Selicrelumab,** or **Control** – by chance. Randomly putting people into these groups makes it more likely that the characteristics of the people in both groups (for example, age, race, 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 this subgroup knew which medicines people were taking. Apart from the different medicines being tested in the **Imprime**, **Isatuximab**, **Selicrelumab**, and **Control** **Groups**, all other aspects of care were the same between the 4 subgroups.

### When and where did the study of this subgroup take place?

These four subgroups are part of a larger study called the MORPHEUS-Colorectal Cancer Study. While the larger study and **Control Group** are still happening, the people in the other subgroups started their treatment in September 2018 or March 2019 and ended in March or August 2020. This summary includes the results between March and August of 2020.

The study took place at 13 study centres in Australia, France, South Korea, Switzerland, and the United States.

## 4. Who was part of these subgroups?

The four subgroups included 49 people with colorectal cancer: 57% were men and 43% were women. They were 45 to 75 years old. Each person had cancer that had spread to other parts of the body, and they 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 **Imprime Group**, **Isatuximab Group**, **Selicrelumab Group,** or **Control Group** by a computer and were given specific treatments. Each table shows what medicines were used to treat people in each subgroup, and when and how the medicines were taken.

| Imprime Group | | | |
|---|---|---|---|
| | **Atezolizumab** | **Imprime PGG** | **Bevacizumab** |
| Number of people taking this medicine | 15 | | |
| When and how the medicines were taken | Injected into a vein on day 1 of every 21-day cycle | Injected into a vein on days 1, 8, and 15 of each 21-day cycle | Injected into a vein 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 | | |

| Isatuximab Group | | |
|---|---|---|
| | **Atezolizumab** | **Isatuximab** |
| Number of people taking this medicine | 15 | |
| When and how the medicines were taken | Injected into a vein on day 1 of every 21-day cycle | Injected into a vein on days 1, 8, and 15 of every 21-day cycle and then every 3 weeks thereafter |
| 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 | |

| Selicrelumab Group | | | |
|---|---|---|---|
| | **Atezolizumab** | **Selicrelumab** | **Bevacizumab** |
| Number of people taking this medicine | 6 | | |
| When and how the medicines were taken | Injected into a vein on days 1 and 15 of every 28-day cycle | Injected just under the skin on day 1 of each 28-day cycle for 1-4 cycles and then every 3 months thereafter | Injected into a vein on days 1 and 15 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 | 13 |
| 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 18 weeks of treatment, researchers found that:

- Of the 49 people collectively in the **Imprime Group**, **Isatuximab Group**, **Selicrelumab Group**, or **Control Group**, no one had their tumours 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, headache) that happen during the study.

- They are described in the summary because the study researchers believe that the side effects may be related to the treatments in the study.
- Not all of the people in this study had all the side effects.
- 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 this study 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 from what is included in the patient leaflets, brochures, or websites for any of the medicines that are used in this study.

Information about common and serious side effects seen in this study are listed below. It is important to note that researchers did not see any new or unusual side effects in this study other than those that have already been found in other studies of each of the medicines that were used.

### Top 6 or more most common side effects that were seen in at least 25 of 100 people (25%)

**Here are the most common side effects seen in the 15 patients treated in the Imprime Group:**

- Reaction to a medicine being infused into a vein: 8 of 15 people (53%)
- Feeling tired (fatigue): 7 out of 15 people (47%)
- Diarrhoea: 6 out of 15 people (40%)
- Poor appetite: 5 of 15 people (33%)
- Pyrexia (fever): 4 out of 15 people (27%)
- Throwing up (vomiting): 4 out of 15 people (27%)

**Here are the most common side effects seen in the 15 patients treated in the Isatuximab Group:**

- Reaction to a medicine being infused into a vein: 11 of 15 people (73%)
- Feeling tired (fatigue): 9 out of 15 people (60%)
- Feeling sick (nausea): 6 out of 15 people (40%)
- Pain in the stomach area (abdominal pain): 4 out of 15 people (27%)
- Chills: 4 out of 15 people (27%)
- Cough: 4 out of 15 people (27%)
- Poor appetite: 4 out of 15 people (27%)

**Here are the most common side effects seen in the 6 patients treated in the Selicrelumab Group:**

- Reaction to injection into a vein: 5 out of 6 people (83%)
- Diarrhoea: 3 out of 6 people (50%)
- Physical weakness or lack of energy: 2 out of 6 people (33%)
- Constipation: 2 out of 6 people (33%)
- Being short of breath: 2 out of 6 people (33%)
- Feeling tired (fatigue): 2 out of 6 people (33%)
- Blood present in the urine (haematuria): 2 out of 6 people (33%)
- Insomnia: 2 out of 6 people (33%)
- Throwing up (vomiting): 2 out of 6 people (33%)
- Neck pain: 2 out of 6 patients (33%)
- Poor appetite: 2 out of 6 (33%)

**Here are the most common side effects seen in the 13 patients treated in the Control Group:**

- Hand-foot syndrome: 8 out of 13 people (62%)
- Feeling tired (fatigue): 6 out of 13 patients (46%)
- Diarrhoea: 5 out of 13 people (38%)
- Feeling sick (nausea): 5 out of 13 people (38%)
- Poor appetite: 5 out of 13 (38%)
- Constipation: 4 out of 13 patients (31%)
- Pain in the stomach area (abdominal pain): 4 out of 13 patients (31%)
- Increased levels of bilirubin in the blood: 4 out of 13 patients (31%)
- Pain in the arms and legs: 4 out of 13 patients (31%)

People taking the medicine combinations in these studies 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 these studies, about 44 out of 49 people (90%) 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:

- 13 out of 15 people (87%) in the Imprime Group
- 13 out of 15 people (87%) in the Isatuximab Group
- 6 out of 6 people (100%) in the Selicrelumab Group
- 12 out of 13 people (92%) 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.

A serious side effect happened in:

- 0 out of 15 people (0%) in the **Imprime Group**
- 5 out of 15 people (33%) in the **Isatuximab Group**
- 3 out of 6 people (50%) in the **Selicrelumab Group**
- 3 out of 13 people (23%) in the **Control Group**

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

A treatment-related serious side effect happened in:

- 0 out of 15 people (0%) in the **Imprime Group**
- 0 out of 15 people (0%) in the **Isatuximab Group**
- 3 out of 6 people (50%) in the **Selicrelumab Group**
- 1 out of 13 people (8%) in the **Control Group**

| **Treatment-related serious side effects reported in this group** | **People in the Selicrelumab Group (6 people)** |
|---|---|
| Diarrhoea | 16.7% (1 out of 6) |
| Throwing up (vomiting) | 16.7% (1 out of 6) |
| Fainting or passing out (syncope) | 16.7% (1 out of 6) |
| Nosebleeds (epistaxis) | 16.7% (1 out of 6) |
| High blood pressure | 16.7% (1 out of 6) |

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

| **Treatment-related serious side effects reported in this group** | **People in the Control Group (13 people)** |
|---|---|
| Tunnel-like hole inside the body between two organs or blood vessels (fistula) | 7.7% (1 out of 13) |

## 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 **Imprime**, **Isatuximab**, or **Selicrelumab Groups**.

- One person in the **Control Group** 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 **Imprime**, **Isatuximab** or **Selicrelumab** **Groups**, no patients stopped taking their medicine because of a related side effect.
- In the **Control Group**, 2 out of 13 people (15%) stopped taking their medicine because of 3 related side effects: increased levels of white blood cells in the blood ('leukocytosis'), sepsis, and tunnel-like hole inside the body between two organs or blood vessels ('fistula').

## 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 one of three combinations of medicines: **atezolizumab with Imprime PGG plus bevacizumab**, **atezolizumab with isatuximab**, or **atezolizumab with selicrelumab plus bevacizumab** 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 from these studies may be different from results from 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 add other people to these subgroups or to do other studies with these medicines?

Currently no other studies are looking at the use of atezolizumab together with **Imprime PGG plus bevacizumab**, **isatuximab**, or **selicrelumab plus bevacizumab** in 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

If you want to learn more about the results from these subgroups, see the following abstracts/posters:

- "Phase Ib/II open-label, randomized evaluation of **atezolizumab (atezo) + Imprime PGG (Imprime) + bevacizumab (bev)** vs **regorafenib (rego)** in MORPHEUS: Microsatellite-stable (MSS) metastatic colorectal cancer (mCRC)." The authors of the poster presented at the American Society of Clinical Cancer (ASCO) 2021 Annual Meeting are Marwan Fakih, James M. Cleary, Yong Sang Hong, Tae-You Kim, Rachael A Safyan, Simon Allen, Lorna Bailey, Edward Cha, Christelle Lenain, Danny Lu, Jochen Schulze, Colby S. Shemesh, and Stefan Zimmermann. The link is here: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.3559.
- "Phase Ib/II open-label, randomized evaluation of efficacy and safety of **atezolizumab plus isatuximab** versus **regorafenib** in MORPHEUS-colorectal cancer." The authors of the poster presented at the American Society of Clinical Oncology Gastrointestinal Cancers (ASCO GI) 2021 Symposium are Jayesh Desai, Marwan Fakih, Katrina Sophia Pedersen, Yong Sang Hong, Neil Howard Segal, Simon Allen, Lorna Bailey, Christelle Lenain, Danny Lu, Pakeeza Zahra Sayyed, Jochen Schulze, and Michael Cecchini. The link is here: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.3_suppl.82.
- "Phase Ib/II open-label, randomized evaluation of **atezolizumab (atezo) + selicrelumab (seli) +** gemcitabine+nab-paclitaxel (gem+nabP) or **bevacizumab (bev)** vs control in MORPHEUS-PDAC, -TNBC and -CRC." The authors of the poster presented at the Society for Immunotherapy of Cancer's (SITC) 2020 are Gulam A. Manji, Nathan Bahary, Vincent Chung, Florence Dalenc, Michel Ducreux, Carlos Gomez-Roca, Seock-Ah Im, Jeremy Kortmansky, Jill Lacy, Neil H. Segal, Olivier Tredan, Olivera Cirovic, Kelly DuPree, Christelle Lenain, Danny Lu, Lidia Robert, Jeffrey Xu, Xiaosong Zhang, and Sung-Bae Kim. The link is here: https://jitc.bmj.com/content/8/Suppl_3/A157.

## 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 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 ClinxicalTrials.gov identifier for this study is: NCT03555149.
- The EudraCT number for this study is: 2017-004566-99.