

Summary of Clinical Trial Results

MORPHEUS Pancreatic Cancer Study: data from a subgroup of previously treated people who received atezolizumab with cobimetinib compared to those who were treated with chemotherapy

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

About This Summary

This is a summary of the results from a small group of people (called a 'subgroup' in this document) who were part of a large clinical trial (called a 'study' in this document) called the MORPHEUS Pancreatic Cancer Study.

This summary has been written for:

- People who were part of this subgroup
- People who are part of the MORPHEUS Pancreatic Cancer Study, and
- Members of the public.

This summary is based on information known at the time that it was written in July 2021.

While the larger MORPHEUS study is still ongoing, the patients in this subgroup started their treatment in July 2017 and ended in June 2019. This summary includes the complete results that were analysed in October 2019.

Key Questions

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

Thank you to our study participants!

As a clinical study participant, you 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 for taking part in this clinical study of atezolizumab with cobimetinib. The part of the study for this subgroup began in July 2017 and finished in October 2019. You and 42 other patients helped researchers find out how safe atezolizumab is and how well it works when used in combination with cobimetinib compared to chemotherapy for people with pancreatic cancer.

As the company that organized and funded this study (Sponsor), we believe it is important for you to know the results of this study. We hope this summary helps you understand and feel proud of the critical role you have played in medical research. If you have questions about the results

outlined in this document, please speak with the study researcher, research nurse, or other team member at your study site.

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 medicines like atezolizumab and cobimetinib. The results of this study 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 to your study researcher before making any decisions about your treatment.**

1. What has happened since this study ended?

The larger MORPHEUS study is still ongoing. However, the part of the study that you participated in – which looked at a subgroup of people who were given either atezolizumab with cobimetinib or chemotherapy took 23 months (almost 2 years) to complete and included people from 3 countries. A total of 28 patients with pancreatic cancer received 840 mg of atezolizumab by injection into a vein every 2 weeks plus 60 mg of cobimetinib by mouth on days 1-21 of each 28-day cycle. Fifteen (15) additional patients with pancreatic cancer had chemotherapy by injection into a vein. This is a summary of the results from these patients. The Sponsor presented early results from this study at the American Association for Cancer Research (AACR) in April 2020, and the final results were presented to health authorities, like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), in March 2020.

2. Why was this research needed?

People who have cancer of the pancreas (pancreatic cancer) that worsens and spreads to other parts of the body do not live for very long.

Current treatments for pancreatic cancer include chemotherapy, which kills cancer cells and stops the cancer from growing. People with pancreatic 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 (shrink the tumour). If the tumour shrinks, even by a little bit, people may be able to manage their cancer better.

One medicine that has helped people with cancer live longer is a cancer 'immunotherapy' medicine called atezolizumab. Cancer immunotherapy medicines work by stimulating your body's immune system to find and fight cancer. Researchers think that these types of medicines might work better to shrink tumours if they are combined with other medicines.

For the subgroup participants, researchers wanted to see if giving people a medicine called cobimetinib with a cancer immunotherapy medicine at the same time would work better than only chemotherapy to shrink their tumours. Cobimetinib is a type of medicine called a kinase inhibitor, and it works by inhibiting proteins called the mitogen-activated protein kinase 1 and 2 (MEK1 and MEK2), which then prevents or slows the growth of cancer. Specifically, researchers wanted to know if treating people who have pancreatic cancer with atezolizumab together with cobimetinib 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 chemotherapy.

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

The results for this subgroup of people helped answer the following important questions:

- How many people had smaller or no tumours after taking their medicine?
- How safe is the combination of atezolizumab plus cobimetinib?
- How many people had side effects and how severe were these side effects?

3. General information about this study

The MORPHEUS pancreatic cancer study is made up of many subgroups. Each subgroup includes people who received one combination of medicines.

The MORPHEUS pancreatic cancer study also includes people at different stages of their treatments. For example, 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 pancreatic cancer study, people enrolled into Stage 1 were receiving second-line treatment and people enrolled into Stage 2 were receiving third-line treatment. People in Stage 1 were put into different study subgroups by chance and received different combinations of medicines depending on which subgroup they were in. If a person from Stage 1 had their cancer get worse, they could be put into Stage 2 to try a different combination of medicines.

What medicines were used to treat people in this subgroup?

All of the people in this subgroup received atezolizumab plus cobimetinib or chemotherapy.

People with pancreatic cancer who were part of this subgroup were split into 3 smaller groups – Group A, Group B and Group C.

- **Group A** and **Group B** are part of Stage 1 and included people receiving second-line treatment for pancreatic cancer whose cancer got worse after chemotherapy.
- **Group C** is part of Stage 2 and included people receiving third-line treatment for pancreatic cancer whose cancer got worse in Stage 1 from another subgroup in the larger study.

People in **Group A** and **Group C** were treated with a medicine called atezolizumab (known by its brand name, TECENTRIQ®) taken together with another medicine called cobimetinib.

- 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.
- Cobimetinib (you say this as 'KOE – bi – ME – ti – nib')
 - This medicine is a kinase inhibitor.
 - 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 protein kinases such as MEK 1 and MEK2 which stops the cancers from growing and also makes them more open to attack by the immune system.
 - Cobimetinib might help atezolizumab work better so people's tumours (cancer) may get smaller.

- People in **Group B** were treated either with (1) a medicine that has already been approved for use called gemcitabine (known by its brand name Gemzar®) plus a commonly used chemotherapy drug called *nab*-paclitaxel (known by its brand name Abraxane®) or (2) a combination of 3 medicines – 5-fluorouracil, leucovorin, and oxaliplatin (also called mFOLFOX6). These are available treatments for people with pancreatic cancer:
- Gemcitabine (you say this as ‘jem – sai – tuh – been’)
 - This medicine is a chemotherapy medicine.
 - Chemotherapy works by stopping cancer cells from separating into new cells, so it blocks the growth of the tumour.
- *nab*-paclitaxel (you say this as ‘nab – pac – lee – tax – el’)
 - This medicine is a chemotherapy medicine.
 - Chemotherapy works by stopping cancer cells from separating into new cells, so it blocks the growth of the tumour.
- mFOLFOX6 (you say this as ‘em – foal – fox – 6’)
 - This medicine is a chemotherapy medicine.
 - Chemotherapy works by stopping cancer cells from separating into new cells, so it blocks the growth of the tumour.

What kind of study was this?

This subgroup is part of a larger study called the MORPHEUS Pancreatic 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. A small number of people in this subgroup took atezolizumab together with cobimetinib, and researchers did medical tests on these people to find out if these 2 medicines taken together had any effect on treating their cancer.

The people in this subgroup were ‘randomised,’ meaning that they were randomly put into two smaller groups – **Group A** or **Group B** – 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 **Groups A/C and Group B**, all other aspects of care were the same between the 3 groups.

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

This subgroup is part of a larger study called the MORPHEUS Pancreatic Cancer Study. While the larger study is still continuing, the people in this subgroup started their treatment in July 2017 and ended in June 2019. This summary includes the results up until October 2019.

The study took place at 12 study centres in 3 countries in Asia, Europe, and North America.

4. Who was part of this subgroup?

This subgroup included 43 people with pancreatic cancer: 44% were men and 56% were women between the ages of 45 and 77 years. 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 this subgroup?

During Stage 1, people in this subgroup were randomly placed in either **Group A** or **Group B** by a computer and were given specific treatments. As part of Stage 2, people were placed in **Group C** if their cancer got worse in Stage 1 from another subgroup. This table shows the 3 groups in the study, what medicines were used to treat each group, and when and how the medicines were taken.

People with pancreatic cancer			
	Group A and C		Group B
	Atezolizumab	Cobimetinib	Chemotherapy
Number of people taking this medicine	14 and 14		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	Gemcitabine and nab-paclitaxel: injected into a vein on days 1, 8, and 15 of every 28-day cycle or 5-fluorouracil: injected into a vein on days 1 and 2 and days 15 and 16 of every 28-day cycle Leucovorin and oxaliplatin: 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		
Target end date of treatment	No target end date. People received treatment until their disease got worse		

6. What were the results for this subgroup?

After 18 weeks of treatment, researchers found that:

- Of the 43 people in this subgroup, no one in **Groups A** and **B** (Stage 1) had their tumours shrink as a result of their treatment, but 2 people in **Group C** (Stage 2) had their tumours shrink while taking atezolizumab plus cobimetinib.

7. What side effects did people in this subgroup 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 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.

Most common side effects

Here are the most common side effects seen in the 14 patients treated in Group A:

- Nausea: 7 out of 14 people (50%)
- Liver, heart, or kidney damage – shown by higher levels of something called ‘AST’ in the blood: 7 out of 14 people (50%)
- Pyrexia (fever): 6 out of 14 people (43%)
- Vomiting: 5 out of 14 people (36%)
- Fatigue: 5 out of 14 people (36%)
- Diarrhoea: 5 out of 14 people (36%)

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

- Nausea: 8 out of 15 people (53%)
- Vomiting: 5 out of 15 people (33%)
- Poor appetite: 5 out of 15 people (33%)
- Abnormally low level of white blood cells: 5 out of 15 people (33%)
- Physical weakness or lack of energy: 5 out of 15 people (33%)

Here are the most common side effects seen in the 14 patients treated in Group C:

- Diarrhoea: 6 out of 14 people (43%)
- Swelling of lower legs and hands: 6 out of 14 people (43%)
- Vomiting: 4 out of 14 people (29%)
- Urinary tract infection: 4 out of 14 people (29%)
- Poor appetite: 4 out of 14 (29%)

People taking the medicine combinations in this study (in either group) 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 3 groups:

During this study, about 33 out of 43 people (77%) 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.

- 11 out of 14 people (79%) in **Group A** had a treatment-related side effect.
- 13 out of 15 people (87%) in **Group B** had a treatment-related side effect.
- 9 out of 14 people (64%) in **Group C** had a treatment-related side effect.

Serious side effects

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

During this study,

- 8 out of 14 people (57%) in **Group A** had a serious side effect.
- 7 out of 15 people (47%) in **Group B** had a serious side effect.
- 7 out of 14 people (50%) in **Group C** had a serious side effect.

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.

Treatment-related serious side effects reported in this study	People in Group A (14 people)	People in Group B (15 people)	People in Group C (14 people)
Low levels of red blood cells or haemoglobin	0	6.7% (1 out of 15)	0
Multiple blood clots in the body	0	6.7% (1 out of 15)	0
Fever and low levels of white blood cells	7.1% (1 out of 14)	0	0
Irregular heartbeat	0	6.7% (1 out of 15)	0
Fever	7.1% (1 out of 14)	13.3% (2 out of 15)	0
Allergic reaction or intolerance to medication	0	6.7% (1 out of 15)	0
Lowered levels of platelets ('platelet count decreased')	0	6.7% (1 out of 15)	0
Clot in a deep vein in the body	0	6.7% (1 out of 15)	0
Inflammation of the pancreas	0	0	7.1% (1 out of 14)
Autoimmune disease of the kidneys	0	0	7.1% (1 out of 14)

Side effects that caused death

Some people 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 **Group A**.

- One person in **Group B** died because of a side effect of multiple blood clots in the body ('disseminated intravascular coagulation, DIC'), which the researchers thought was related to one of the study medicines.
- One person in **Group C** died because of a side effect of infection of the mouth or throat, which the researchers thought was not related to one of 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 **Group A**, no patient stopped taking their medicine because of a related side effect.
- In **Group B**, 1 out of 15 people (7%) stopped taking their medicine because of related side effects: multiple blood clots in the body ('disseminated intravascular coagulation, DIC') and clot in a deep vein in the body ('deep vein thrombosis, DVT').
- In **Group C**, 2 out of 14 people (14%) stopped taking their medicine because of 3 related side effects: fungal infection of the blood ('systemic candida'), autoimmune disease of the kidneys ('autoimmune nephritis'), and abnormal liver function test.

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

The information in this summary is from part of the larger MORPHEUS Pancreatic Cancer Study. These results are for a subgroup of patients who were given either atezolizumab together with cobimetinib or chemotherapy. These results have helped researchers learn more about how atezolizumab interacts with other medicines for the treatment of people with pancreatic 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 this study 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 study researchers before making any decisions about your treatment.**

9. Are there plans to add other people to this subgroup or to do other studies with these medicines?

Currently no other studies are looking at the use of atezolizumab together with cobimetinib in pancreatic cancer.

10. Where can I find more information?

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

- <https://www.clinicaltrials.gov/ct2/show/NCT03193190>
- <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-004126-42>
- <https://forpatients.roche.com/en/trials/cancer/pancreatic-cancer/a-study-of-multiple-immunotherapy-based-treatment-combinations-i2.html>

If you want to learn more about the results from this subgroup, see the following abstract/poster:

“Phase Ib/II open-label, randomized evaluation of atezolizumab + cobimetinib vs control in MORPHEUS-NSCLC (non-small cell lung cancer), MORPHEUS-PDAC (pancreatic ductal adenocarcinoma) and MORPHEUS-GC (gastric cancer).” The authors of the poster presented at American Association for Cancer Research (AACR) 2020 are Byoung Chul Cho, Nathan Bahary, Johanna Bendell, Enriqueta Felip, Melissa Johnson, Yoon-Koo Kang, Farah Louise Lim, Teresa Macarulla, Gulam Manji, Do-Youn Oh, Osama Rahma, Simon Allen, Edward Cha, Denise Cotting, Hans-Joachim Helms, Jan Pintoffl, Pakeeza Sayyed, Xiaosong Zhang, and Kyu-pyo Kim. The link is here: https://cancerres.aacrjournals.org/content/80/16_Supplement/CT201

Who can I contact if I have questions about this subgroup or the larger MORPHEUS Pancreatic Cancer Study?

If you have more questions, visit [ForPatients.roche.com](https://forpatients.roche.com) and fill out the contact form.

If you were part of this subgroup and have any questions about the results, talk to your study researchers or staff at the hospital or clinic where you were treated.

If you have questions about your own treatment, talk to the study researchers in charge of your treatment.

Who organised and paid for this subgroup and the larger MORPHEUS Pancreatic Cancer Study?

The MORPHEUS Pancreatic Cancer Study and this subgroup were organised and paid for by F. Hoffmann-La Roche Ltd whose headquarters are in Basel, Switzerland. The medicine cobimetinib was provided by F. Hoffmann-La Roche.

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 Pancreatic Ductal Adenocarcinoma (Morpheus-Pancreatic Cancer)”

The study is also known as MORPHEUS-PDAC.

- The protocol number for this study is: WO39608.
- The ClinicalTrials.gov identifier for this study is: NCT03193190.
- The EudraCT number for this study is: 2016-004126-42.