MORPHEUS Urothelial Carcinoma Study: data from subgroups of previously treated people who received atezolizumab with magrolimab, niraparib, or tocilizumab compared with those who were treated with atezolizumab

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

About This Summary

This is a summary of the results from small groups of people (called 'subgroups') who were part of a large clinical trial (or 'study') called the MORPHEUS Urothelial Carcinoma Study.

This summary has been written for:

- People who were part of the subgroups
- People who are part of the MORPHEUS Urothelial Carcinoma Study, and
- Members of the public

This summary is based on information known at the time it was written in February 2023.

While the larger MORPHEUS study is still ongoing, the people in these subgroups started their treatment in June 2019 and received their last treatment in July 2021. This summary includes the complete results that were analysed in April 2022.

Key Questions

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 magrolimab, niraparib, or tocilizumab.

The part of the study that included these subgroups began in June 2019, and the last treatment was given in July 2021. The subgroups were: (1) the **magrolimab group**, (2) the **niraparib group**, (3) the **tocilizumab group**, and (4) the **control group**, which received **atezolizumab alone**. The 76 patients in these subgroups helped researchers find out how safe atezolizumab is and how well it works when used in combination with **magrolimab**, **niraparib**, or **tocilizumab** compared with **atezolizumab alone** for people with previously treated urothelial carcinoma.

As the company that organized and funded this study (the '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 important role you have played in medical research. If you have questions about the

results outlined in this document, please speak with the doctor, research nurse, or another 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 plus magrolimab**, **atezolizumab plus niraparib**, and **atezolizumab plus tocilizumab**. 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 only this summary. Always talk to your doctor 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 subgroups of people who were given **atezolizumab alone** or with either **magrolimab**, **niraparib**, or **tocilizumab**—took 25 months (about 2 years) to complete and included people from 20 study centres across 7 countries.

The **magrolimab group** included 16 people who were given **atezolizumab plus magrolimab**.

The **niraparib group** included 15 people who were given **atezolizumab plus niraparib**.

The **tocilizumab group** included 15 people who were given **atezolizumab plus tocilizumab**.

The **control group** included 30 people who were given **atezolizumab alone**.

This is a summary of the results from these subgroups.

2. Why was this research needed?

People who have bladder cancer (urothelial carcinoma) that worsens and spreads to other parts of the body have a shorter life expectancy.

Current treatments for urothelial carcinoma include chemotherapy, which kills cancer cells and stops the cancer from growing, and a group of medicines called 'cancer immunotherapy,' which work by stimulating the body's immune system to find and fight cancer. However, in some people, these medicines may work for only a short time, or the cancer keeps growing even with treatment. Researchers think that cancer immunotherapy might work better to shrink tumours if it is combined with other medicines.

For subgroup participants, researchers wanted to see if giving people a cancer immunotherapy combined with another medicine at the same time would work better to shrink their tumours than the single cancer immunotherapy alone. These other medicines are called magrolimab, niraparib and tocilizumab.

- Magrolimab is a type of immunotherapy that works by inhibiting a protein called CD47, which helps the immune system find and attack the cancer cells
- Niraparib is a type of medicine called a PARP inhibitor. PARP proteins help cells repair damaged DNA. Preventing cells from repairing DNA by inhibiting PARP can cause the cells to die. Cancer cells are more likely to have damaged DNA than healthy cells, so this medicine is expected to kill cancer cells but leave healthy cells alone

- Tocilizumab is a type of immunotherapy that works by inhibiting a protein called IL-6. This blocks inflammation and helps the immune system attack the cancer cells

Specifically, researchers wanted to know if treating people who have urothelial carcinoma with atezolizumab together with magrolimab, niraparib, or tocilizumab would help them live longer or lengthen the amount of time before their cancer got worse, compared with people who were treated with only atezolizumab.

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 the 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 long did it take for people's cancer to get worse?
- How long did people in the study live?
- How well did people tolerate the combinations of atezolizumab with magrolimab, niraparib, or tocilizumab?
- How many people had side effects and how severe were the side effects?

3. General information about this study

The MORPHEUS Urothelial Carcinoma Study is made up of many subgroups. Each subgroup includes people who received one combination of medicines.

The MORPHEUS Urothelial Carcinoma Study also includes people at different stages of their treatments. People were put into different study subgroups by chance and received different combinations of medicines depending on which subgroup they were in. If a person's cancer got worse, they could try a different combination of medicines.

What medicines were used to treat people in these subgroups?

To form the subgroups in this summary, people with urothelial carcinoma whose cancer got worse after the first recommended treatment (first-line medicines) were split into smaller groups—the **magrolimab group**, **niraparib group**, **tocilizumab group**, or **control group**.

The first 3 subgroups looked at a medicine called 'atezolizumab' (known by its brand name, TECENTRIQ®) taken together with an additional medicine.

- **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 stop the immune system from attacking the cancer. Atezolizumab releases this blockage, meaning that the immune system becomes able to fight the cancer cells again
  - When people take atezolizumab, their tumour (cancer) may get smaller

People in the **magrolimab group** were treated with **atezolizumab** taken together with a medicine called **magrolimab**.

- **Magrolimab** (you say this as 'muh-grow-luh-mab')
  - This medicine is a type of immunotherapy

- The body's immune system fights diseases like cancer, but cancer cells can hide from the immune system. Magrolimab blocks a protein called CD47 to help uncover the cancer cells, meaning that the immune system can find and attack the cancer

People in the **niraparib group** were treated with **atezolizumab** taken together with a medicine called **niraparib** (known by its brand name, ZEJULA®).

- **Niraparib** (you say this as 'nih–rap–uh–rib')
  - This medicine is a PARP inhibitor
  - Niraparib blocks proteins called PARP1 and PARP2 that repair damaged DNA
  - Cancer cells are more likely to have damaged DNA than healthy cells
  - Without the proteins needed for DNA repair, cancer cells die

People in the **tocilizumab group** were treated with **atezolizumab** taken together with a medicine called **tocilizumab** (known by its brand name, ACTEMRA®).

- **Tocilizumab** (you say this as 'toe–suh–li–zuh–mab')
  - This medicine is a type of immunotherapy
  - The body's immune system fights diseases like cancer. Tocilizumab blocks a protein called IL-6 that can cause inflammation and help stop the immune system from fighting cancer cells. This helps the immune system attack the cancer cells and destroy the tumour

People in the **control group** were treated with only **atezolizumab**.

What kind of study was this?

These subgroups are part of a larger study called the MORPHEUS Urothelial Carcinoma 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 well tolerated the combination of medicines are. People in these subgroups took **atezolizumab** together with **magrolimab**, **niraparib**, or **tocilizumab**, and researchers did medical tests on these people to find out if these medicines taken together had any effect on their cancer. The results in these subgroups were compared with results in the **control group**, which included people who took only **atezolizumab**.

The people in these subgroups were 'randomised,' meaning that they were randomly put into 4 smaller groups—the **magrolimab group**, **niraparib group**, **tocilizumab group**, or **control group**—by chance. Randomly putting people into these groups makes it more likely that the characteristics of the people in the groups (such as 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 this subgroup knew which medicines people were taking. Apart from the different medicines being tested in the groups, all other aspects of care were the same between the 4 groups.

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

These subgroups are part of a larger study called the MORPHEUS Urothelial Carcinoma Study. While the larger study is still going on, the people in this subgroup started their treatment in June 2019 and had their last treatment in July 2021. This summary includes the results up until April 2022.

The study took place at 20 study centres in 6 countries in Asia, Europe, and North America.

4. Who was part of these subgroups?

These subgroups included a total of 76 people between the ages of 46 and 87 years with urothelial carcinoma; 78% were men and 22% were women. Most people had cancer that had spread to other parts of the body, and everyone had already been given treatment that had not worked or had stopped working. Two people left the study before they took any of the study medicines; these people are not included in the results shown below.

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

People in these subgroups were randomly placed in either the **magrolimab group**, **niraparib group**, **tocilizumab group**, or **control group** by a computer and were given specific treatments. This table shows the subgroups, what medicines were used to treat each group and when and how the medicines were taken.

Magrolimab group (15 people)		
	Atezolizumab	**Magrolimab**
When and how the medicines were taken	Injected into a vein on Days 1 and 15 of every 28-day cycle	Cycles 1 and 2: Injected into a vein on Days 1, 8, 15 and 22 of each 28-day cycle Cycle 3+: Injected into a vein on Days 1 and 15 of each 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	

Niraparib group (15 people)		
	Atezolizumab	**Niraparib**

When and how the medicines were taken	Injected into a vein on Day 1 of every 21-day cycle	Given by mouth on Days 1-21 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	

Tocilizumab group (15 people)		
	Atezolizumab	**Tocilizumab**
When and how the medicines were taken	Injected into a vein on Days 1 and 15 of every 28-day cycle	Injected into a vein on Day 1 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	

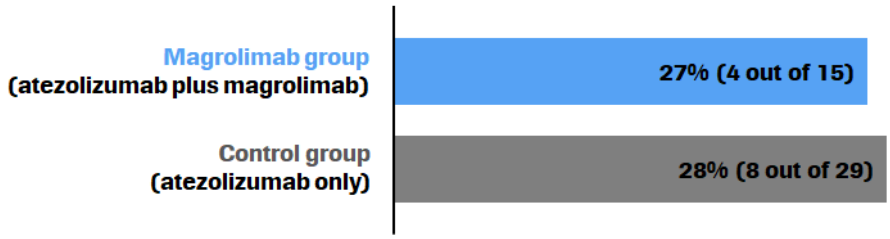
Control group (29 people)	
	Atezolizumab
When and how the medicine was taken	Injected into a vein on Day 1 of every 21-day cycle
How long treatment was expected to last	Until their disease got worse or treatment was stopped for safety reasons
Target end date of treatment	No target end date. People received treatment until their disease got worse

6. What were the results for these subgroups?

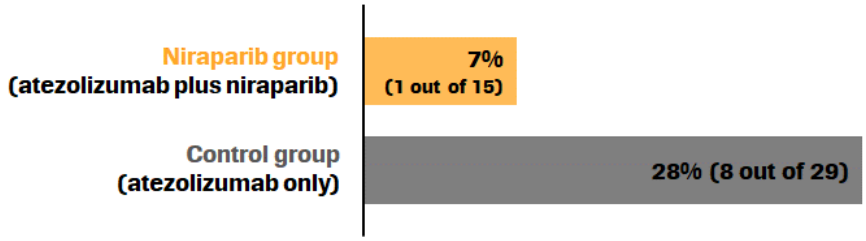
How many people had smaller or no tumours after taking their medicine?

Researchers found that adding magrolimab, niraparib, or tocilizumab to atezolizumab did not result in more people having their tumours get smaller or go away compared with atezolizumab alone.

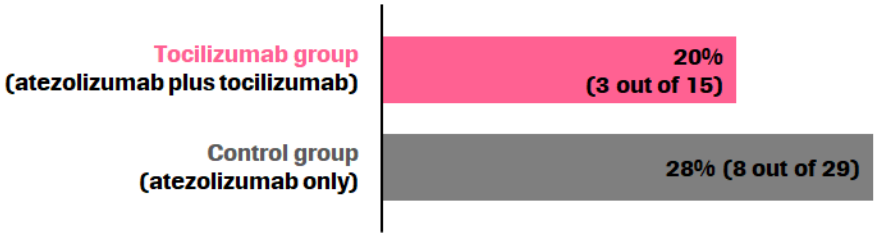
How many people had smaller or no tumours after treatment in the magrolimab group?



How many people had smaller or no tumours after treatment in the niraparib group?



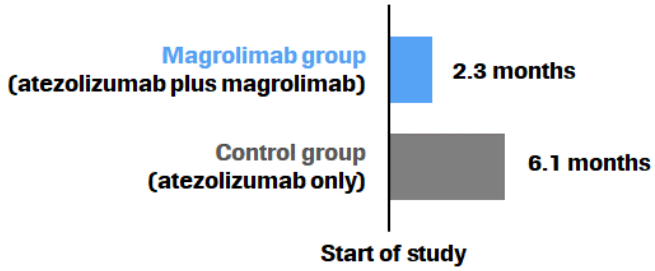
How many people had smaller or no tumours after treatment in the tocilizumab group?



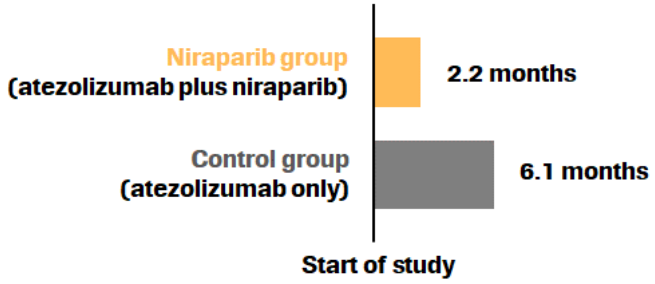
How long did it take for people's cancer to get worse?

Compared with atezolizumab alone, researchers found that adding magrolimab, niraparib, or tocilizumab to atezolizumab did not increase the time it took for people's cancer to worsen.

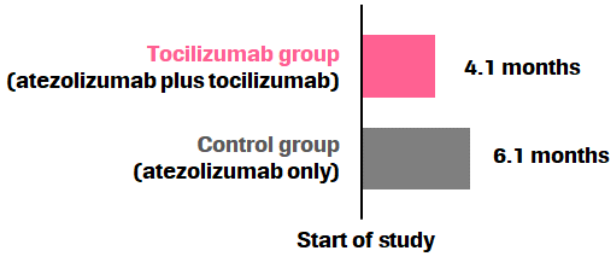
On average, how long did it take for people's cancer to get worse in the magrolimab group?



On average, how long did it take for people's cancer to get worse in the niraparib group?



On average, how long did it take for people's cancer to get worse in the tocilizumab group?



How long did people in the study live?

Researchers found that adding magrolimab, niraparib, or tocilizumab to atezolizumab did not increase how long people in the study lived compared with people who took atezolizumab alone.

- People in the **magrolimab group** lived for around 21.8 months on average after starting the medicines
- People in the **niraparib group** lived for around 8.6 months on average after starting the medicines
- People in the **tocilizumab group** lived for around 6.3 months on average after starting the medicines
- In the **control group**, the average time people lived after starting the medicine could not be calculated because fewer than 50% had died

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.

- Not all of the people in this study had all of the side effects
- Side effects can range from 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 other studies of the same medicines. The side effects listed here may also be different from the ones included in the patient leaflets, brochures, or websites for any of the medicines used in this study.

Information about the common and serious side effects seen in this study can be found below. It is important to note that researchers did not see any new or unusual side effects in this study. All side effects seen had already been reported 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 15 patients treated in the magrolimab group:

Most common side effects	Magrolimab group (15 people)
Anaemia (low number of red blood cells)	60% (9 out of 15)
Pyrexia (fever)	40% (6 out of 15)
Urinary tract infection	40% (6 out of 15)
Fatigue (tiredness)	33% (5 out of 15)
Haematuria (blood in the urine)	33% (5 out of 15)
Arthralgia (joint pain)	27% (4 out of 15)
Decreased appetite	27% (4 out of 15)
Diarrhoea	27% (4 out of 15)
Myalgia (muscle pain)	27% (4 out of 15)
Pruritus (itchy skin)	27% (4 out of 15)

Here are the most common side effects seen in the 15 patients treated in the niraparib group:

Most common side effects	Niraparib group (15 people)
Anaemia (low number of red blood cells)	47% (7 out of 15)
Fatigue (tiredness)	33% (5 out of 15)
Decreased appetite	27% (4 out of 15)
Kidney damage (shown by higher levels of a protein called 'creatinine' in the blood)	27% (4 out of 15)
Nausea	27% (4 out of 15)

Here are the most common side effects seen in the 15 patients treated in the tocilizumab group:

Most common side effects	**Tocilizumab group (15 people)**
Liver damage (shown by higher levels of a protein called 'ALT' in the blood)	40% (6 out of 15)
Liver, heart or kidney damage (shown by higher levels of a protein called 'AST' in the blood)	40% (6 out of 15)
Constipation	33% (5 out of 15)

Here are the most common side effects seen in the 29 patients treated in the control group:

Most common side effects	Control group (29 people)
Decreased appetite	24% (7 out of 29)
Pruritus (itchy skin)	24% (7 out of 29)
Anaemia (low number of red blood cells)	21% (6 out of 29)
Urinary tract infection	21% (6 out of 29)
Fatigue (tiredness)	21% (6 out of 29)

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 15 people (53%) in the **magrolimab group** had a serious side effect
- 7 out of 15 people (47%) in the **niraparib group** had a serious side effect
- 7 out of 15 people (47%) in the **tocilizumab group** had a serious side effect
- 9 out of 29 people (31%) in the **control group** 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	Magrolimab group (15 people)	Niraparib group (15 people)	Tocilizumab group (15 people)	Control group (29 people)
Anaemia (low levels of red blood cells)	7% (1 out of 15)	7% (1 out of 15)	0	0
Cytokine release syndrome (too aggressive immune response)	7% (1 out of 15)	0	0	0
Diarrhoea	7% (1 out of 15)	0	0	0
Infusion-related reaction (allergic reaction to or	7% (1 out of 15)	0	0	0

intolerance of medication when first given)				
Interstitial lung disease (scarring of the lungs)	7% (1 out of 15)	0	0	0
Myalgia (muscle pain)	7% (1 out of 15)	0	0	0
Pancytopenia (low levels of red blood cells, white blood cells, and platelets)	7% (1 out of 15)	0	0	0
Pneumonitis (inflammation of lung tissue)	7% (1 out of 15)	0	0	0
Pyrexia (fever)	7% (1 out of 15)	0	0	0
Acute kidney injury (kidney failure)	0	7% (1 out of 15)	0	0
Cardio-respiratory arrest (loss of heart and lung function)	0	7% (1 out of 15)	0	0
Decreased platelet count (lowered levels of platelets)	0	13% (2 out of 15)	0	0
Psoriasis (inflammation of the skin)	0	0	0	3% (1 out of 29)

Side effects that caused death

One person in the **niraparib group** died from cardio-respiratory arrest (loss of heart and lung function) that may or may not have been related to one of the study medicines. There were no fatal side effects in the other 3 subgroups.

Stopping the medicines 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 **magrolimab group**, 3 out of 15 people (20%) stopped taking their medicine because of related side effects
- In the **niraparib group**, 2 out of 15 people (13%) stopped taking their medicine because of related side effects
- None of the patients in the **tocilizumab group** or the **control group** stopped taking their medicine because of related side effects

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

The information in this summary is from part of the larger MORPHEUS Urothelial Carcinoma Study. These results are for subgroups of patients who were given either atezolizumab alone or

together with magrolimab, niraparib, or tocilizumab. These results have helped researchers learn more about how atezolizumab interacts with other medicines for the treatment of people with previously treated urothelial carcinoma.

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 the results of other studies of the same medicines. **This means that you should not make medical decisions based only on this 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 plus magrolimab, niraparib, or tocilizumab in urothelial carcinoma.

10. Where can I find more information?

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

- https://clinicaltrials.gov/ct2/show/NCT03869190
- https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-004634-28
- https://forpatients.roche.com/en/trials/cancer/bladder-cancer/a-study-evaluating-the-efficacy-and-safety-of-multiple—45851.html

If you want to find out more about the results of this study, the full title of the relevant scientific paper is: “Atezolizumab Plus Magrolimab, Niraparib, or Tocilizumab in Platinum-Refractory Metastatic Urothelial Carcinoma: A Phase Ib/II Open-Label, Randomized Umbrella Study”. The authors of the scientific paper are: Alexandra Drakaki, Thomas Powles, Aristotelis Bamias, Juan Martin-Liberal, Sang Joon Shin, Jae-Lyun Lee and others. The paper is published in the journal Clinical Cancer Research (online ahead of print; doi: 10.1158/1078-0432.CCR-23-0798).

Who can I contact if I have questions about these subgroups or the larger MORPHEUS Urothelial Carcinoma Study?

If you have more questions, visit ForPatients.roche.com , click on ‘Contact Us’ at the bottom of the page, and fill out the contact form.

If you were part of these subgroups and have any questions about the results, talk to your doctor or staff at the hospital or clinic where you were treated.

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

Who organised and paid for these subgroups and the larger MORPHEUS Urothelial Carcinoma Study?

The MORPHEUS Urothelial Carcinoma Study and these subgroups were organised and paid for by F. Hoffmann-La Roche Ltd, whose headquarters are in Basel, Switzerland. Atezolizumab and tocilizumab were provided by F. Hoffmann-La Roche Ltd, magrolimab was provided by Gilead Sciences, Inc., and niraparib was provided by GlaxoSmithKline plc.

Full title of the study and other identifying information

The full title of the study is: "Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatments and Combinations in Patients With Urothelial Carcinoma (MORPHEUS-UC)."

The study is also known as MORPHEUS-UC.

- The protocol number for this study is: WO39613
- The ClinicalTrials.gov identifier for this study is: NCT03869190
- The EudraCT number for this study is: 2017-004634-28