

Research Sponsor: AstraZeneca AB

Drug Studied: MEDI4736 and tremelimumab

Study Title: A study to find out how MEDI4736 given alone or with tremelimumab works in participants with cancer of the bladder or urinary system that has spread and cannot be removed by surgery

Thank you!

Thank you to the participants for taking part in the clinical study for the study drugs MEDI4736 and tremelimumab.

All of the participants helped researchers learn more about MEDI4736 to help people with cancer of the bladder or urinary system that has spread and cannot be removed by surgery.

AstraZeneca AB sponsored this study and believes it is important to share the results of the study with you and the public. An independent non-profit organization called CISCRP helped prepare this summary of the study results for you. We hope it helps you understand and feel proud of your important role in medical research.

If you participated in the study and have questions about the results, please speak with the study doctor or staff at your study site.

Overview

> Why was the research needed?

Researchers are looking for a better way to treat cancer of the bladder or urinary system that has spread and cannot be removed by surgery. Before a drug can be approved for people to get, researchers do clinical studies to find out how it works and how safe it is.

> What treatments did the participants take?

The participants in this study got either:

- MEDI4736 with tremelimumab
- MEDI4736 alone
- Standard chemotherapy

> What were the results of the study?

The main questions the researchers wanted to answer in this study were:

- **Did MEDI4736 with tremelimumab help the participants live longer than chemotherapy?**

Overall, the researchers found that the participants who got MEDI4736 with tremelimumab did not live longer compared with the participants who got chemotherapy.

- **Did MEDI4736 alone help the participants with PD-L1 high cancer live longer than chemotherapy?**

Overall, the researchers found that the participants who got MEDI4736 alone did not live longer compared with the participants who got chemotherapy.

- **Did the participants getting MEDI4736 alone or with tremelimumab have less severe symptoms?**

The researchers found that the participants getting MEDI4736 alone had less severe symptoms during treatment compared with those getting chemotherapy. But, they did not find that the participants getting MEDI4736 with tremelimumab had a change in symptoms compared with those getting chemotherapy.

- **What medical problems did the participants have during the study?**

There were 73.2% of participants who had medical problems that the study doctors thought might be related to the study drug during the study. The most common medical problems were fatigue and nausea. More details about the results of this study are included later in this summary.

> Where can I learn more about this study?

You can find out more information about this study on the websites listed on the last page. When a full report of the study results is available, it can also be found on those websites.



Who took part in the study?

The researchers asked for the help of people with cancer of the bladder or urinary system that had spread and could not be removed by surgery. The men and women in this study were 32 to 89 years old when they joined.

The participants had not had chemotherapy before they joined the study. They had at least 1 tumor measuring at least 1 centimeter, which is just under half an inch. They were able to do at least some light physical activity or work. The participants who joined the study were expected to live for at least 12 more weeks at the time that they joined.

The study included 1,032 participants in Australia, Austria, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, Israel, Italy, Japan, Mexico, the Netherlands, Poland, Portugal, Russian Federation, South Korea, Spain, Taiwan, Turkey, the United Kingdom, and the United States.



Why was the research needed?

Researchers are looking for a better way to treat cancer of the bladder or urinary system that has spread and cannot be removed by surgery. Cancer of the bladder or urinary system is also called urothelial cancer. Before a drug can be approved for people to get, researchers do clinical studies to find out how safe it is and how it works.

In people with cancer, the body is not able to control the growth of cells. The extra cells can form tumors. When cancer progresses to a late stage, tumors spread to other parts of the body or grow beyond the organ where they started. Sometimes there are too many tumors or they are too difficult to remove by surgery.

Normally, the immune system can help stop tumors from growing. But in people with urothelial cancer, the proteins on the tumor cells can interact with certain proteins on the immune cells. This may stop the immune cells from recognizing the tumor cells and being able to attack them.

The study drugs, MEDI4736 and tremelimumab, were each designed to stop the tumor cells from interacting with some of these proteins. MEDI4736 does this by attaching to a protein called PD-L1 on tumor cells. Tremelimumab does this by attaching to a protein called CTLA-4 on tumor cells. This lets the immune cells recognize the tumor cells again and help stop the tumor from growing.

In this study, the researchers wanted to learn about MEDI4736 alone or with tremelimumab in a large number of participants. The participants had urothelial cancer that had spread and could not be removed by surgery. The researchers in this study wanted to compare MEDI4736 with and without tremelimumab to standard chemotherapy. They also wanted to find out if the participants had any medical problems during the study.



What was the purpose of this study?

The main questions the researchers wanted to answer in this study were:

- > Did MEDI4736 with tremelimumab help the participants live longer than chemotherapy?
- > Did MEDI4736 alone help the participants with PD-L1 high cancer live longer than chemotherapy?
- > Did the participants getting MEDI4736 with or without tremelimumab have less severe symptoms?
- > What medical problems did the participants have during the study?

The answers to these questions are important to know before other studies can be done to find out if MEDI4736 helps improve the health of people with urothelial cancer that has spread and cannot be removed by surgery.



What treatments did the participants take?

In this study, the participants got either:

- > MEDI4736 with tremelimumab
- > MEDI4736 alone
- > Standard chemotherapy

Each treatment was given through a needle into a vein. This is known as an intravenous infusion, also known as an IV infusion.

The doses of MEDI4736 and tremelimumab were measured in milligrams, also known as mg.

This was an “open-label” study. This means the participants, researchers, study doctors, and other study staff knew what each participant was getting.

A computer program was used to randomly choose the treatment each participant got. This helps make sure the groups are chosen fairly. Researchers do this so that comparing the results of each treatment is as accurate as possible.

The participants got their study treatment until their cancer got worse, the study doctors decided they should stop study treatment, or they left the study.

The chart below shows the treatments the participants got.

Group	Treatments and doses
MEDI4736 with tremelimumab (342 participants)	<ul style="list-style-type: none">• MEDI4736 1,500 mg and tremelimumab 75 mg• Every 4 weeks, 4 doses overall then <ul style="list-style-type: none">• MEDI4736 1,500 mg• Every 4 weeks until disease got worse
MEDI4736 alone (346 participants)	<ul style="list-style-type: none">• MEDI4736 1,500 mg• Every 4 weeks until disease got worse
Chemotherapy (344 participants)	Chosen by the study doctor <ul style="list-style-type: none">• Cisplatin + gemcitabine or <ul style="list-style-type: none">• Carboplatin + gemcitabine

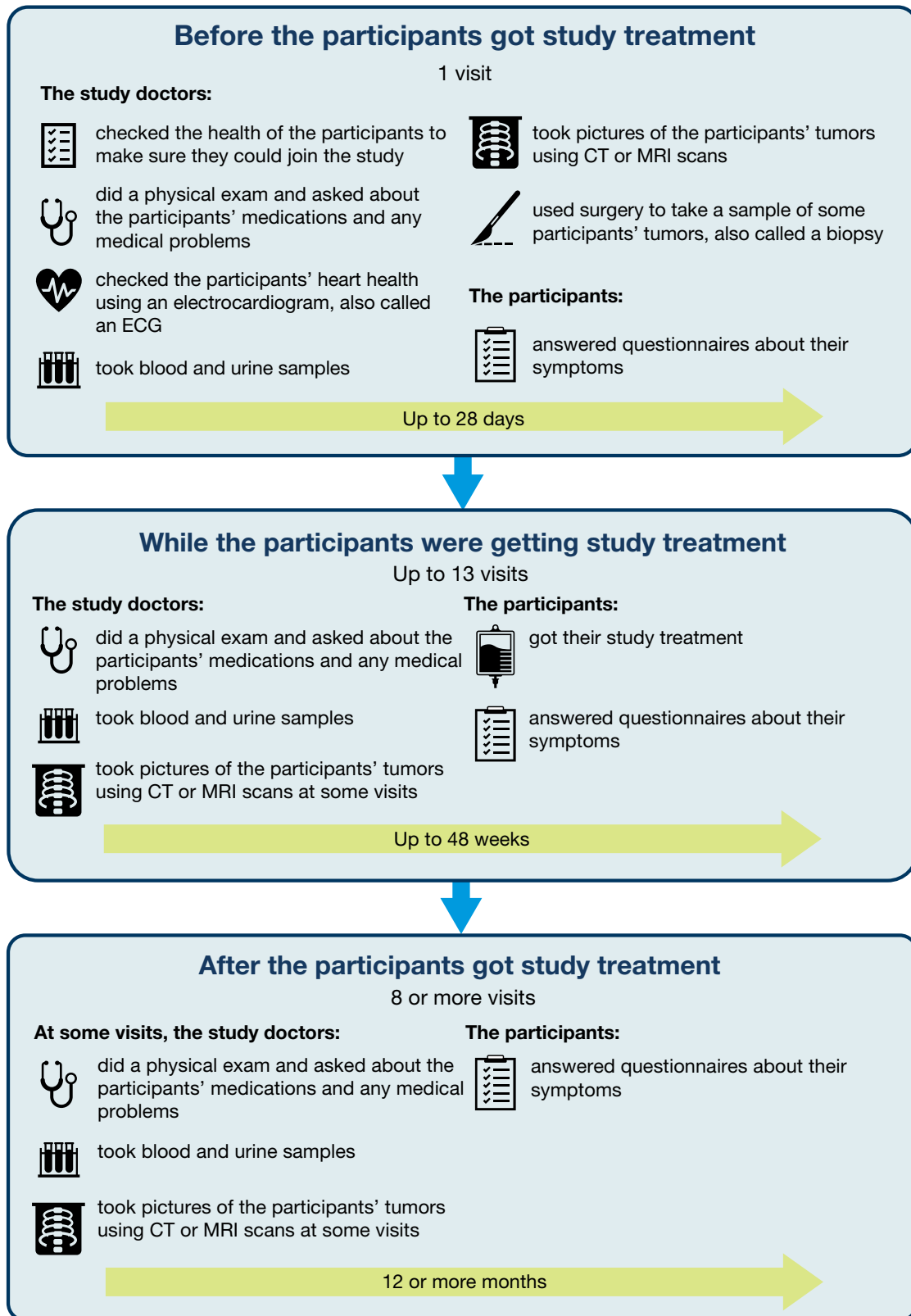


What happened during the study?

The participants were in the study until their cancer got worse, the study doctors thought they should stop study treatment, or they left for another reason. But, the entire study took over 4 years to finish.

The study started in November 2015 and ended in January 2020.

The chart below shows what happened during the study.





What were the results of the study?

This is a summary of the main results from this study overall. The results each participant had might be different and are not in this summary. A full list of the questions researchers wanted to answer can be found on the websites listed at the end of this summary. When a full report of the study results is available, it can also be found on these websites.

Researchers look at the results of many studies to decide which treatments work best and are safest. Other studies may provide new information or different results. Always talk to a doctor before making any treatment changes.

Did MEDI4736 with tremelimumab help the participants live longer than chemotherapy?

Overall, the researchers found that the difference between the participants who got MEDI4736 with tremelimumab and those who got chemotherapy was small. It was too small for the researchers to know if MEDI4736 with tremelimumab helped the participants live longer.

To answer this question, the researchers counted the number of months the participants lived with their cancer after getting study treatment. They calculated the median number of months for each group. A median is the middle number in a set of numbers. It is between the lowest and highest numbers.

The median number of months that the participants lived for after study treatment was:

- > 15.1 months for the participants who got MEDI4736 with tremelimumab
- > 12.1 months for the participants who got chemotherapy

Did MEDI4736 alone help the participants with PD-L1 high cancer live longer than chemotherapy?

The researchers wanted to know how MEDI4736 alone affected participants with a certain type of urothelial cancer called PD-L1 high. This is because people with this type of cancer have a large amount of the PD-L1 protein on their tumor cells.

There were 209 participants who got MEDI4736 and 207 participants who got chemotherapy who had PD-L1 high cancer.

Overall, the researchers found that in the participants with PD-L1 high cancer, the difference between those who got MEDI4736 alone and those who got chemotherapy was small. It was too small for the researchers to know if MEDI4736 alone helped these participants live longer.

To answer this question, the researchers counted how many months the participants lived with their cancer after getting study treatment. They calculated the median number of months for each group.

The median number of months that the participants with PD-L1 high cancer lived for after study treatment was:

- > 14.4 months for the participants who got MEDI4736 alone
- > 12.1 months for the participants who got chemotherapy

Did the participants getting MEDI4736 alone or with tremelimumab have less severe symptoms?

The researchers found that the participants getting MEDI4736 alone had less severe symptoms during treatment compared with those getting chemotherapy. They found that the participants getting MEDI4736 with tremelimumab did not have a change in symptoms compared with those getting chemotherapy.

To answer this question, the researchers kept track of the participants' symptoms and how they felt by asking them to complete a questionnaire called Functional Assessment of Cancer Therapy – Bladder, also known as FACT-BL. The researchers gave the participants "scores" based on their answers to the FACT-BL questionnaire. They compared the scores throughout the study. A bigger change in FACT-BL score meant that the participants' symptoms were more severe. The scores were measured in points.

The researchers found that the participants' FACT-BL scores changed by an average of:

- > 4.7 points in the participants getting **MEDI4736 alone**
- > 7.2 points in the participants getting **MEDI4736 with tremelimumab**
- > 8.8 points in the participants getting **chemotherapy**

The study doctors also used some of the participants' answers from the FACT-BL questionnaire to get a score called FACT-BL Trial Outcome Index, also known as FACT-BL TOI. A bigger change in FACT-BL TOI score meant that the participants' symptoms were more severe. The researchers compared the scores throughout the study.

The researchers found that the participants' FACT-BL TOI scores changed by an average of:

- > 3.9 points in the participants getting **MEDI4736 alone**
- > 5.5 points in the participants getting **MEDI4736 with tremelimumab**
- > 7.2 points in the participants getting **chemotherapy**



What medical problems happened during the study?

This section is a summary of the medical problems the participants had during the study that the study doctors thought might be related to the study treatments. These medical problems are called “adverse reactions”. An adverse reaction is considered “serious” when it is life-threatening, causes lasting problems, or requires hospital care.

These adverse reactions may or may not be caused by the study treatments. A lot of research is needed to know whether a treatment causes an adverse reaction. These adverse reactions have been, and will continue to be, reviewed together with all of the available data for the study treatments.

The websites listed at the end of this summary may have other information about adverse reactions or other medical problems that happened during this study.

There were 34 participants who did not finish getting all of their doses of study treatment. So, the results below are for 998 participants.

Did any adverse reactions happen during this study?

	MEDI4736 with tremelimumab (out of 340 participants)	MEDI4736 alone (out of 345 participants)	Chemotherapy (out of 313 participants)
How many participants had adverse reactions?	75.0% (255)	55.9% (193)	90.4% (283)
How many participants had serious adverse reactions?	22.9% (78)	8.7% (30)	16.0% (50)
How many participants stopped taking study treatment due to adverse reactions?	15.6% (53)	6.1% (21)	12.5% (39)

What serious adverse reactions happened during this study?

The most common serious adverse reactions were diarrhea and fever.

The table below shows the serious adverse reactions that happened in 1.0% or more of participants during the study. There were other serious adverse reactions, but these happened in fewer participants.

Most common serious adverse reactions

Serious adverse reaction	MEDI4736 with tremelimumab (out of 340 participants)	MEDI4736 alone (out of 345 participants)	Chemotherapy (out of 313 participants)
Diarrhea	4.1% (14)	0.0% (0)	0.3% (1)
Inflammation of the large intestine	2.1% (7)	0.0% (0)	0.0% (0)
Fever	1.5% (5)	0.0% (0)	1.6% (5)
Lung infection	1.2% (4)	0.0% (0)	0.0% (0)
Pituitary gland not working properly	1.2% (4)	0.0% (0)	0.0% (0)
Damage to the kidneys	0.9% (3)	0.0% (0)	1.3% (4)
Vomiting	0.3% (1)	0.0% (0)	1.3% (4)
Anemia	0.0% (0)	0.0% (0)	2.2% (7)
Decreased numbers of blood cells that help form blood clots	0.0% (0)	0.0% (0)	1.9% (6)
Very low numbers of blood cells that help form blood clots	0.0% (0)	0.0% (0)	1.6% (5)
Decreased numbers of a type of white blood cell called neutrophils	0.0% (0)	0.0% (0)	1.3% (4)
Infection of the urinary tract (may include kidneys and bladder)	0.0% (0)	0.0% (0)	1.3% (4)

There were 0.5% of participants who died because of serious adverse reactions. This was 5 out of 998 participants.

- > • 0.6% of participants getting **MEDI4736 with tremelimumab** died because of a serious adverse reaction. This was 2 out of 340 participants.
- > • 0.6% of participants getting **MEDI4736 alone** died because of a serious adverse reaction. This was 2 out of 345 participants.
- > • 0.3% of participants getting **chemotherapy** died because of a serious adverse reaction. This was 1 out of 313 participants.

What adverse reactions happened during this study?

The most common adverse reactions were fatigue and nausea.

The table below shows the adverse reactions that happened in 10.0% or more of participants during the study. There were other adverse reactions, but these happened in fewer participants.

Most common adverse reactions

Adverse reaction	MEDI4736 with tremelimumab (out of 340 participants)	MEDI4736 alone (out of 345 participants)	Chemotherapy (out of 313 participants)
Itching	22.9% (78)	10.4% (36)	3.5% (11)
Diarrhea	21.2% (72)	6.7% (23)	10.5% (33)
Fatigue	14.4% (49)	11.9% (41)	27.2% (85)
Decreased appetite	7.4% (25)	6.7% (23)	19.2% (60)
Nausea	4.7% (16)	7.8% (27)	40.9% (128)
Anemia	2.1% (7)	1.7% (6)	41.9% (131)



How has this study helped patients and researchers?

This study helped researchers learn more about how MEDI4736 with or without tremelimumab worked in participants with urothelial cancer that had spread and could not be removed by surgery.

Researchers look at the results of many studies to decide which treatments work best and are safest. This summary shows only the main results from this one study. Other studies may provide new information or different results.

Further clinical studies with MEDI4736 are planned.



Where can I learn more about this study?

You can find more information about this study on the websites listed below. If more information about the study results is available, it can also be found here.

- > www.clinicaltrials.gov. Once you are on the website, type **"NCT02516241"** into the search box and click **"Search"**.
- > www.clinicaltrialsregister.eu. Once you are on the website, click "Home and Search", then type **"2015-001633-24"** in the search box and click **"Search"**.
- > www.AstraZenecaClinicalTrials.com. Once you are on the website, type **"D419BC00001"** into the search box, and click **"Find a Study"**.

Full Study Title: Phase III, Randomized, Open-Label, Controlled, Multi-Center, Global Study of First-Line MEDI4736 Monotherapy and MEDI4736 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer

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EudraCT Number: 2015-001633-24

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The phone number for the AstraZeneca Information Center is +1-877-240-9479 and the email is information.center@astrazeneca.com.

Thank you!

Clinical study participants and their families belong to a large community of people who take part in clinical research around the world. They help researchers answer important health questions and find medical treatments for patients.



The Center for Information & Study on Clinical Research Participation (CISCRP) is a non-profit organization focused on educating and informing the public about clinical research participation. CISCRP is not involved in recruiting participants for clinical studies, nor is it involved in conducting clinical studies.

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