

# Treatment of muscle-invasive urothelial cancer with nivolumab (CheckMate 274 study): a plain language summary

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## Summary

### What is this summary about?

This is a summary of a paper published in a medical journal that describes the results of a study called CheckMate 274. This study looked at a new treatment for muscle-invasive urothelial cancer, a type of cancer found in the urinary tract that has spread from the inner lining of the urinary tract or bladder and into the surrounding muscle wall where it can then spread to other parts of the body.

The standard treatment for muscle-invasive urothelial cancer is surgery to remove affected parts of the urinary tract. However, cancer returns in more than half of people after this surgery. Adjuvant therapy is given to people after surgery with muscle-invasive urothelial cancer with a goal to reduce the risk of the cancer coming back; however, at the time this study started, there was no standard adjuvant treatment.

### What happened in the study?








In the CheckMate 274 study, researchers compared nivolumab with a placebo as an adjuvant treatment for people with muscle-invasive urothelial cancer. The aim of the study was to understand how well nivolumab worked to reduce the chance of the cancer returning after surgery. The study also looked at what side effects (unwanted or unexpected results or conditions that are possibly related to the use of a medication) people had with treatment.

### What do the results mean?

The results showed that people who received nivolumab versus placebo:

- Survived longer before the cancer was detected again, including people who had programmed death ligand-1 (shortened to PD-L1) on their cancer cells.
- Survived longer before a secondary cancer outside of the urinary tract was detected.
- Experienced no differences in health-related quality of life (the impact of the treatment on a person's mental and physical health).
- Had similar side effects to the people who received nivolumab in other studies.

### How to say (double-click on the icon to play sound)...

- **Adjuvant:** A-joo-vunt 
- **Nivolumab:** nih-VOL-yoo-mab 
- **Urothelial:** YOOR-oh-THEE-lee-ul 
- **Immunotherapy:** IH-myoo-noh-THAYR-uh-pee 
- **Chemotherapy:** KEE-moh-THAYR-uh-pee 
- **Urethra:** yoo-REE-thruh 
- **Ureter:** YER-eh-ter 

## Who sponsored this study?

This study was sponsored by Bristol Myers Squibb and Ono Pharmaceutical. Bristol Myers Squibb would like to thank the people with muscle-invasive urothelial cancer who volunteered to take part in this study and their families, as well as the CheckMate 274 investigators and study teams. Nivolumab is licensed by Bristol Myers Squibb.

## Who is this article for?

This summary of the original article was written for people who want to learn more about clinical research in urothelial cancer and about the results of the CheckMate 274 study.

## Where can I find the original article on which this summary is based?

You can read the original article titled 'Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma', which was published in the *New England Journal of Medicine*, for free at: <https://doi.org/10.1056/NEJMoa2034442>

## What is muscle-invasive urothelial cancer?

Urothelial cancer is the 10th most common cancer in the world and is a type of cancer in the urinary tract. This includes the following body parts: the kidneys, renal pelvis, ureters, bladder, and the urethra (see diagram for further details). Muscle-invasive urothelial cancer happens when urothelial cancer has spread from the inner lining of the renal pelvis, ureters, bladder, or the urethra and into the nearby muscle wall. Without treatment, muscle-invasive urothelial cancer will spread to other parts of the body.

## What treatments are used for muscle-invasive urothelial cancer?

The standard treatment for muscle-invasive urothelial cancer is surgery to remove the affected body parts, such as the bladder, ureters, and/or kidneys and the surrounding lymph nodes. However, cells from the cancer can spread to other parts of the body before the surgery (known as metastases) and start to grow a new tumor. These metastases, or secondary cancers, can be difficult to find in the body at the time of surgery. A secondary cancer happens in more than half of people with urothelial cancer after they have had surgery.

Chemotherapy (medicines to slow the growth of or kill cancer cells) is often used along with surgery to kill remaining cancer cells and decrease the chance of the cancer coming back after the original tumor is removed. Chemotherapy given before surgery is called "neoadjuvant" chemotherapy. A commonly used neoadjuvant chemotherapy is a medicine called cisplatin (also called cisplatin-based neoadjuvant chemotherapy). Not all people are able to take or want to take cisplatin-based neoadjuvant chemotherapy, including almost half of the people in this study. Chemotherapy given after surgery is called "adjuvant" chemotherapy. Adjuvant therapy is given to people with muscle-invasive urothelial cancer with a goal to reduce the risk of the cancer coming back; however, at the time this study was started, there was no standard adjuvant chemotherapy.



## The urinary system

**Kidney:** the body parts that filter the blood to remove waste and make urine to remove that waste

**Renal pelvis:** the area at the center of the kidneys that collects urine and funnels it to the ureters

**Ureters:** the tubes that connect the kidneys and the bladder

**Bladder:** the organ that stores urine. Roughly 95% of urothelial cancers start in the bladder

**Urethra:** the tube that connects to the bladder and allows urine to leave the body

**Stage 1:** urothelial cancer is only within the connective tissue of the bladder

**Stage 2:** urothelial cancer has spread into the muscle wall of the bladder

- Bladder lining

- Connective tissue

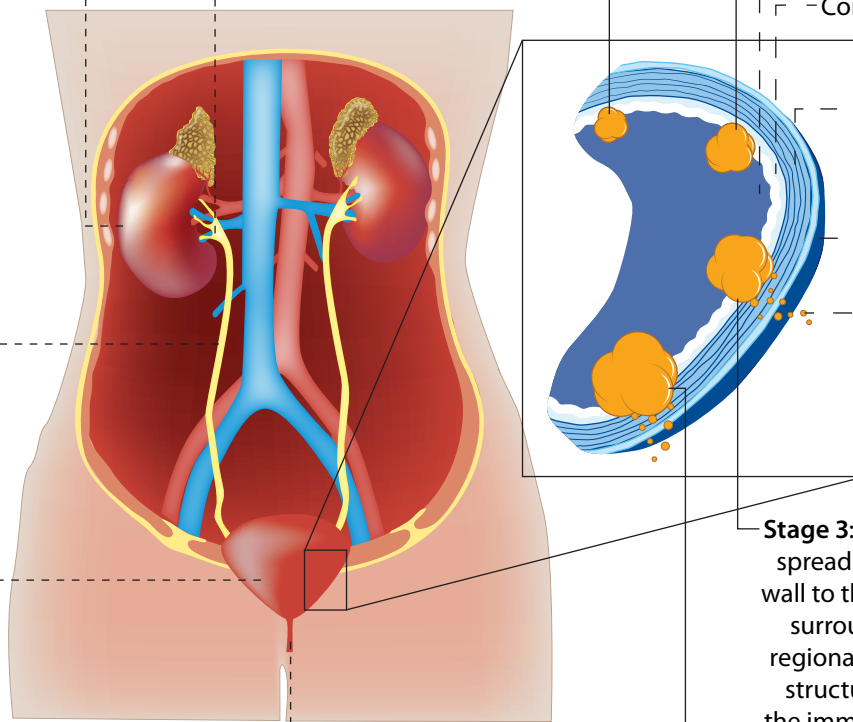
- Muscle

- Fat

Metastatic cells

**Stage 3:** urothelial cancer has spread through the muscle wall to the fatty layer of tissue surrounding the bladder regional lymph nodes (small structures that are part of the immune system and filter out infection and cancer cells), and/or nearby organs (i.e., prostate, uterus, vagina)

**Stage 4:** urothelial cancer has spread from the inner lining into the muscle wall of the bladder, uterus, renal pelvis, and/or traveled to other parts of the body



## What was the CheckMate 274 study?

In the CheckMate 274 study, researchers compared nivolumab with a **placebo**, as an adjuvant treatment for people with muscle-invasive urothelial cancer. They wanted to understand whether nivolumab worked to kill remaining cancer cells and reduce the chance of the cancer returning after surgery. The study also looked at the side effects people had with treatment.



### **Placebo:** (pluh-see-bo)

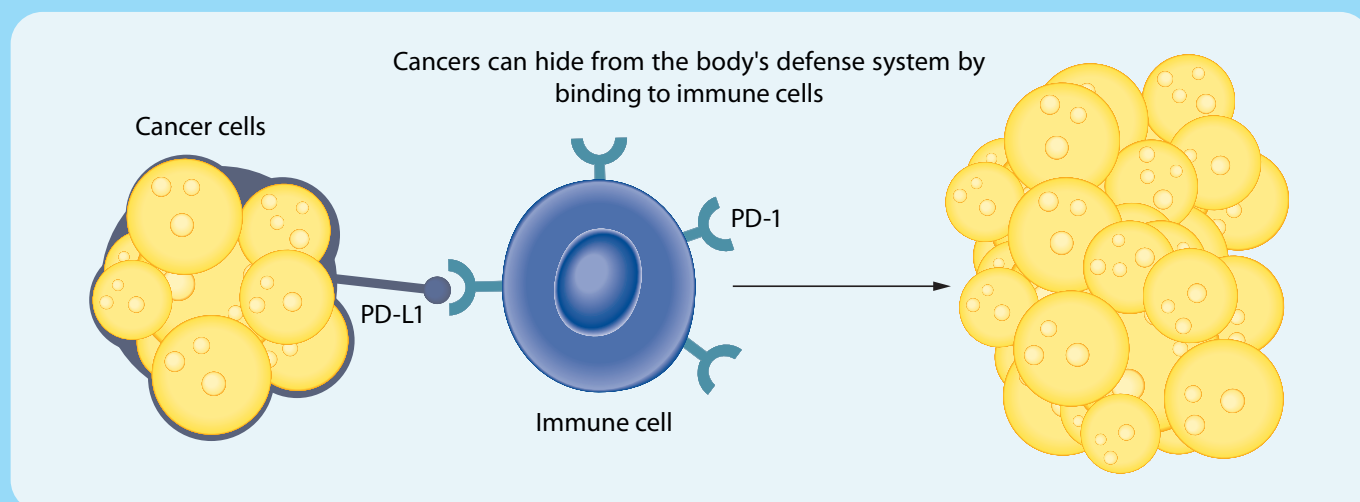
A substance that does not contain active medicine but is identical in appearance to a study drug that is being researched in a clinical trial.

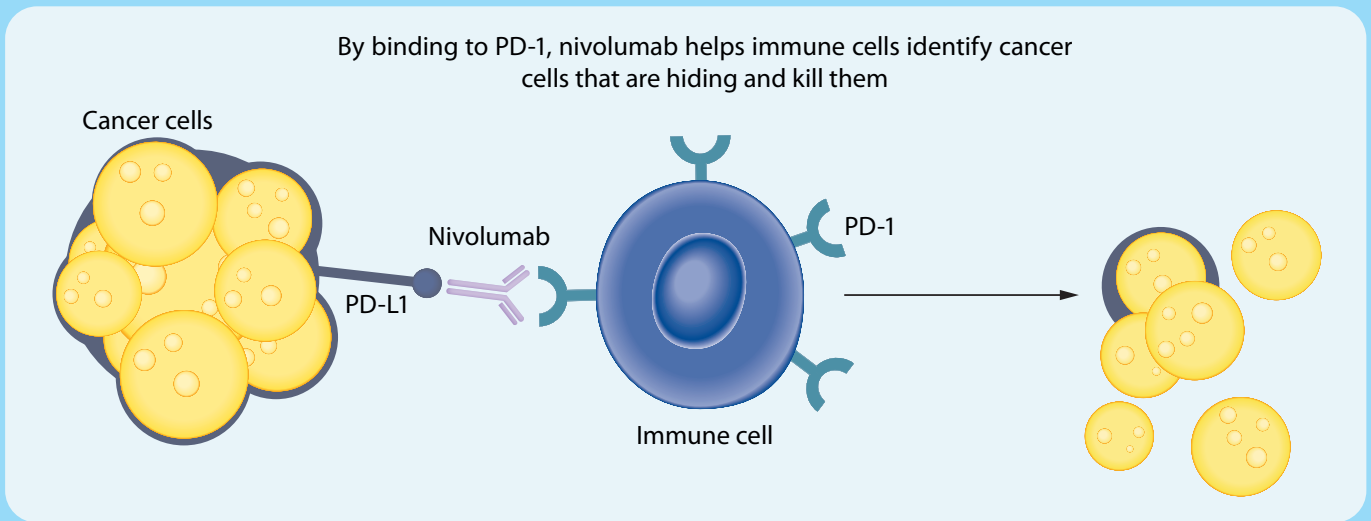
## What is nivolumab?

Nivolumab is a type of cancer treatment called immunotherapy. Nivolumab works differently from chemotherapy. Chemotherapy is a chemical that is toxic to all cells, while nivolumab works in a more selective way. Some cancer cells have large amounts of a protein called programmed death ligand-1 (shortened to PD-L1). PD-L1 helps cancer cells to hide from the body's defense system by binding to a protein called programmed death receptor-1 (shortened to PD-1) on immune cells to inactivate them.

By binding to PD-1, nivolumab stops PD-L1 on the cancer cells from binding to immune cells. This helps the immune cells to identify and kill the cancer cells. This means that nivolumab can potentially reduce or stop cancer growth. Nivolumab has been studied in different types of cancer including urothelial cancer.

## How does nivolumab work?





### What did the CheckMate 274 study look at?

The aim of the study was to compare treatment with nivolumab or a placebo in adults with muscle-invasive urothelial cancer who had recently received surgery to remove the tumor. The goals of this study were to:



Find out how long a person survived and was free of the urothelial cancer returning if they received adjuvant nivolumab compared to those who received placebo treatment. This is called disease-free survival (shortened to DFS) and was the main goal of the study.

Measure DFS in people whose cancer tested positive for PD-L1. In this study, the researchers counted a person's cancer as testing positive for PD-L1 if at least 1 of 100 or more of their cancer cells had PD-L1 on them.



Find out how long a person survived without developing a secondary cancer (also known as recurrence-free survival; shortened to RFS).

Determine the side effects people experienced with treatment, and the impact of the treatment on a person's mental and physical health (health-related quality of life).



## What did this study investigate?



**What patient outcomes were studied?**



**What was measured?**



**What do the results mean?**



**Disease-free survival (DFS)**

Time that a person survived and was free from the cancer returning after starting the treatment

A longer time means that the treatment is more likely to stop the cancer from returning



**DFS in people who had PD-L1 protein on their cancer cells**

DFS in people who had measurable amounts (1% or more) of PD-L1 protein on their cancer cells

Researchers wanted to know if having lots of PD-L1 on their cancer cells made people more likely to have a longer DFS with nivolumab treatment



**Recurrence-free survival (RFS) without developing secondary cancers**

Time that a person survived and was free of cancer returning outside of the urinary tract

A longer time means that the treatment is more likely to stop secondary cancers from developing



**Side effects**

All side effects that occurred during the study were recorded

Side effects can range in severity; however, they may or may not have been caused by the treatments people received during the study

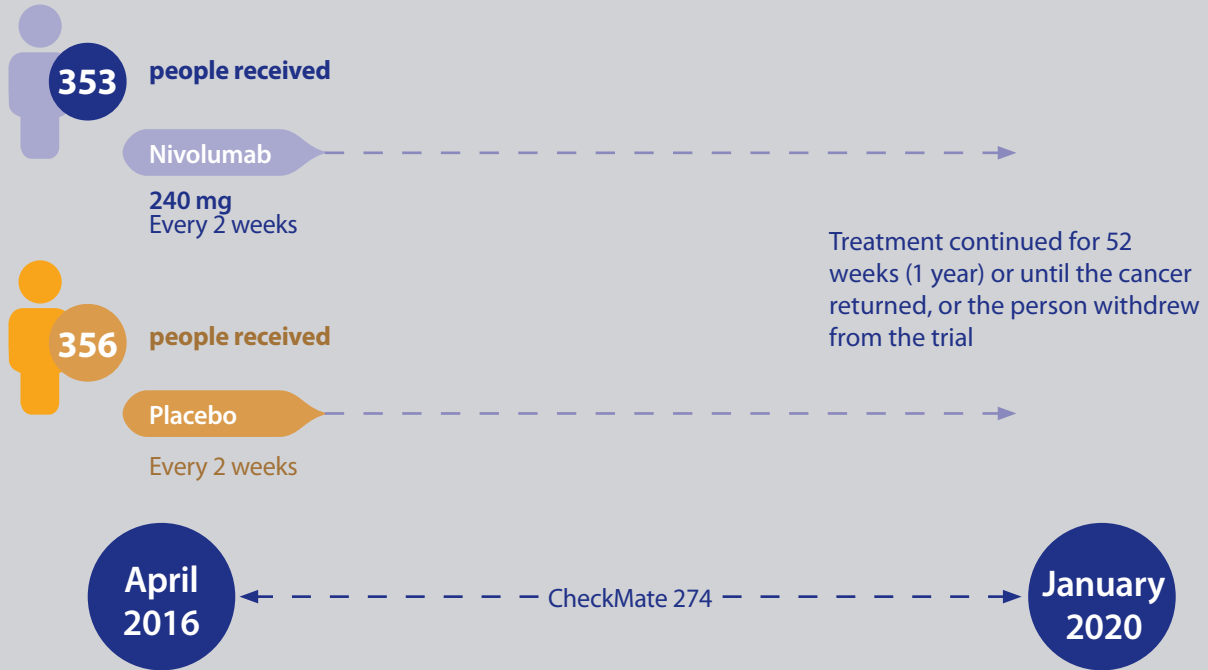


**Health-related quality of life surveys**

These questionnaires are used to measure the health-related quality of life of adults with cancer

Health-related quality of life measures the degree to which an individual is healthy, comfortable and able to participate in or enjoy life events

The study started with a screening period so doctors could check people’s health to make sure they could take part in the study and were cancer-free following surgery to remove the affected body parts. After the screening period, people who could enter the trial were randomly assigned their treatment (this means that the treatment they received was decided by chance). Their treatment was given as an unlabeled 30-minute infusion into a vein through a needle so that they didn’t know what their treatment was.

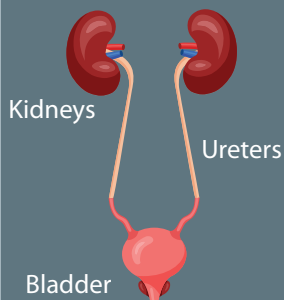


## Who could take part in this study?

Participants shared the following characteristics...

- Men and women  
**18 years +**
- Muscle-invasive urothelial cancer
- With or without cisplatin-based neoadjuvant chemotherapy

Had surgery to remove the affected body parts and nearby lymph nodes within the last 4 months



Had a high risk of cancer returning



Were cancer-free for at least 4 weeks before starting the trial



Also, they must have had tumor tissue from their surgery that could be tested for PD-L1. People were not allowed to take part in the study if they had surgery to remove only part of the bladder or part of the kidneys, or adjuvant chemotherapy or radiation therapy after surgery to remove the bladder.

## Where did this study take place?

The study took place at hospitals in 30 countries across the world:

Argentina  
Australia  
Austria  
Belgium  
Brazil  
Canada  
Chile  
China  
Columbia  
Denmark

France  
Germany  
Greece  
Ireland  
Israel  
Italy  
Japan  
Republic of Korea  
Mexico  
Netherlands

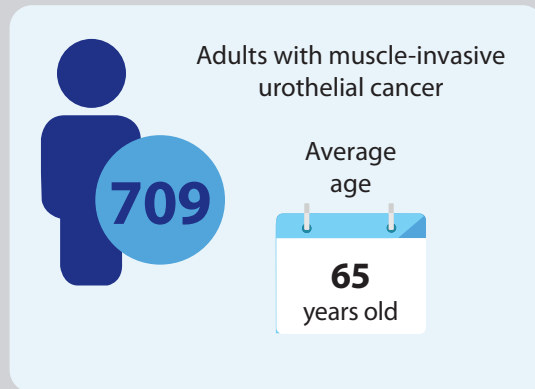
Peru  
Poland  
Romania  
Russian Federation  
Spain  
Sweden  
Switzerland  
Taiwan  
United Kingdom  
United States of America



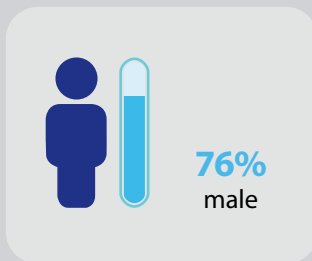


## Who participated in this study?

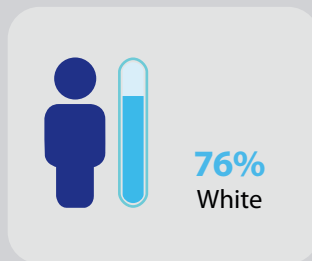
People who took part in this study were....



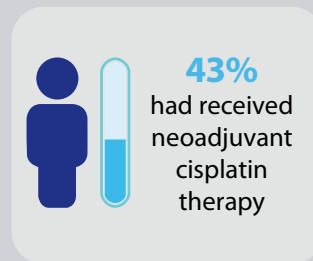
### Gender



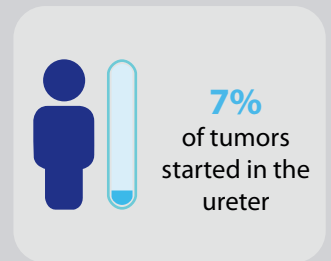
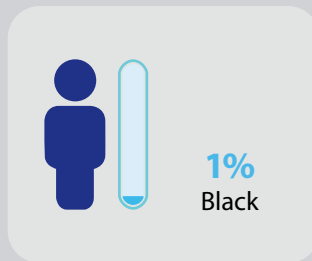
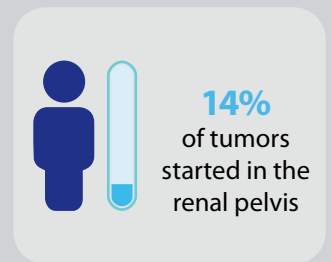
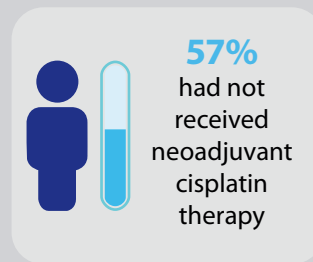
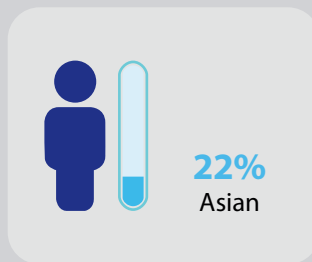
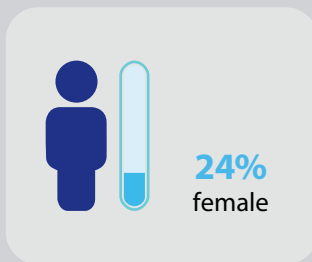
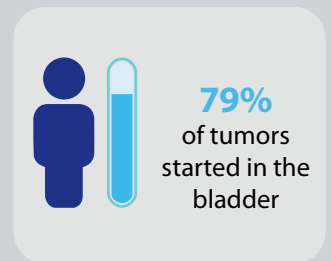
### Race



### Prior treatment



### Tumor location

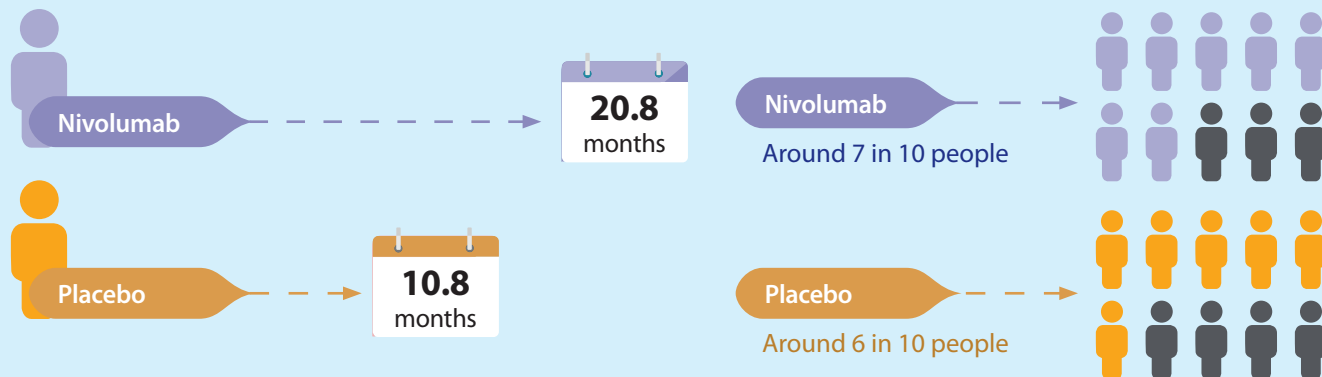


## What were the results of the study?

### Disease-free survival (DFS) and recurrence-free survival (RFS)

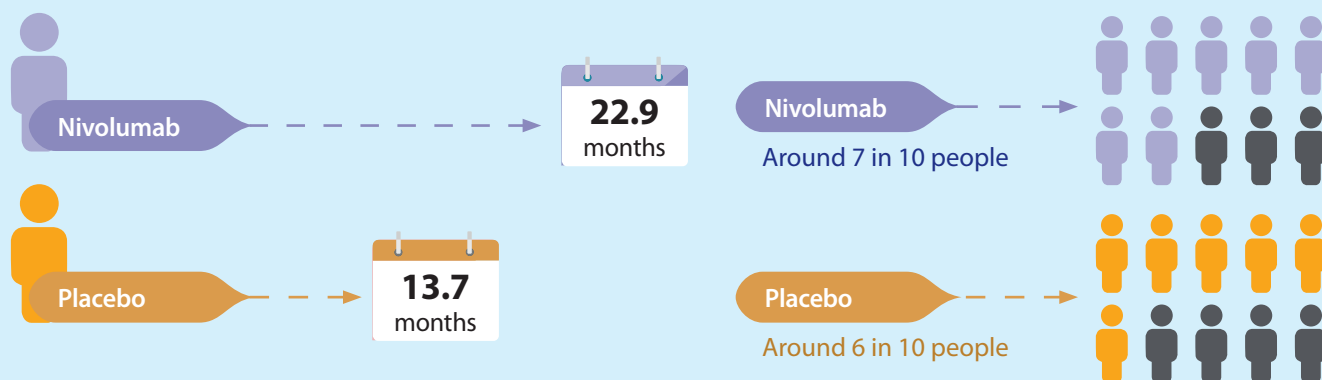
Compared with those who received a placebo, people who received nivolumab had:

- A longer median cancer-free time (DFS)
- A higher percentage of people who were cancer-free at 6 months



The median DFS is the time by which half the people in a clinical trial are alive and cancer free

- A longer median length of time without developing a secondary cancer (RFS) outside the urinary tract
- More people free of a secondary cancer developing outside the urinary tract at 6 months



The median RFS is the time by which half the people in a clinical trial are alive and without signs or symptoms of a secondary cancer

People with PD-L1 protein on their cancer cells and who received nivolumab had a longer median cancer-free time (DFS) and a higher percentage of people who were cancer free at 6 months than those with the protein PD-L1 on their cancer cells who took a placebo.



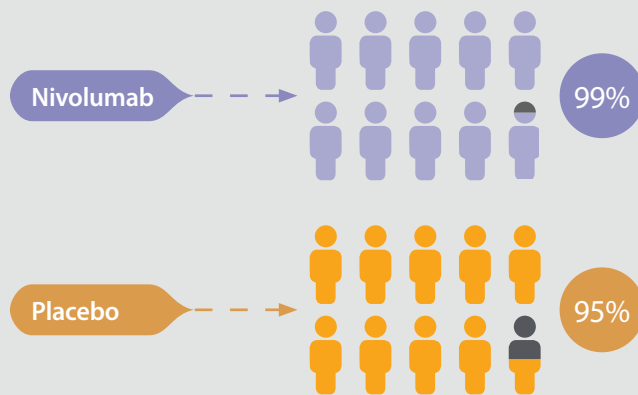
### Quality of life

No differences were observed in the health-related quality of life between people who received nivolumab and those who received a placebo.

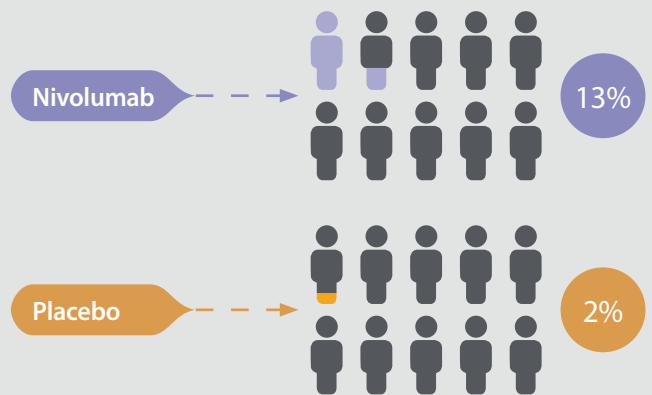
## What were the most common side effects?

More people receiving nivolumab experienced side effects compared with those taking placebo. Side effects can range in severity and are classified as mild, moderate, severe or life-threatening. It is important to note that side effects may or may not be caused by the treatment people receive during the study.

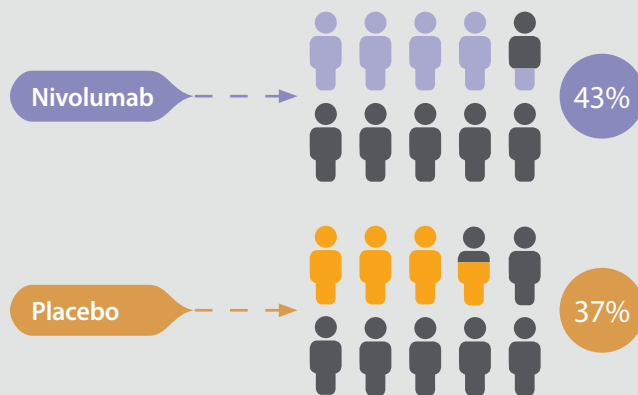
### Percentage of people who had at least 1 side effect during the study:



### Percentage of people who had to stop treatment because of any side effects:



### Percentage of people who experienced more severe side effects (requiring treatment, hospitalization and/or were life threatening):



### Number of deaths due to treatment:



Pruritus (itching)



23%

Nivolumab

12%

Placebo

Fatigue (extreme tiredness)



17%

Nivolumab

12%

Placebo

Diarrhea (loose or watery bowel movements)



17%

Nivolumab

11%

Placebo

Rash



15%

Nivolumab

6%

Placebo

Increased lipase levels (digestive enzymes that the pancreas releases; increased levels can be a sign of pancreas inflammation)



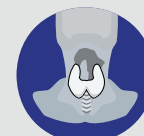
10%

Nivolumab

6%

Placebo

Hypothyroidism (a condition where the thyroid gland doesn't make enough thyroid hormone to keep the body functioning normally)



10%

Nivolumab

1%

Placebo

### What were the most common severe side effects?

Increased lipase levels

Lipase and amylase are digestive enzymes that the pancreas releases; increased levels can be a sign of pancreas inflammation

5%

Nivolumab

3%

Placebo

Increased amylase levels

4%

Nivolumab

1%

Placebo

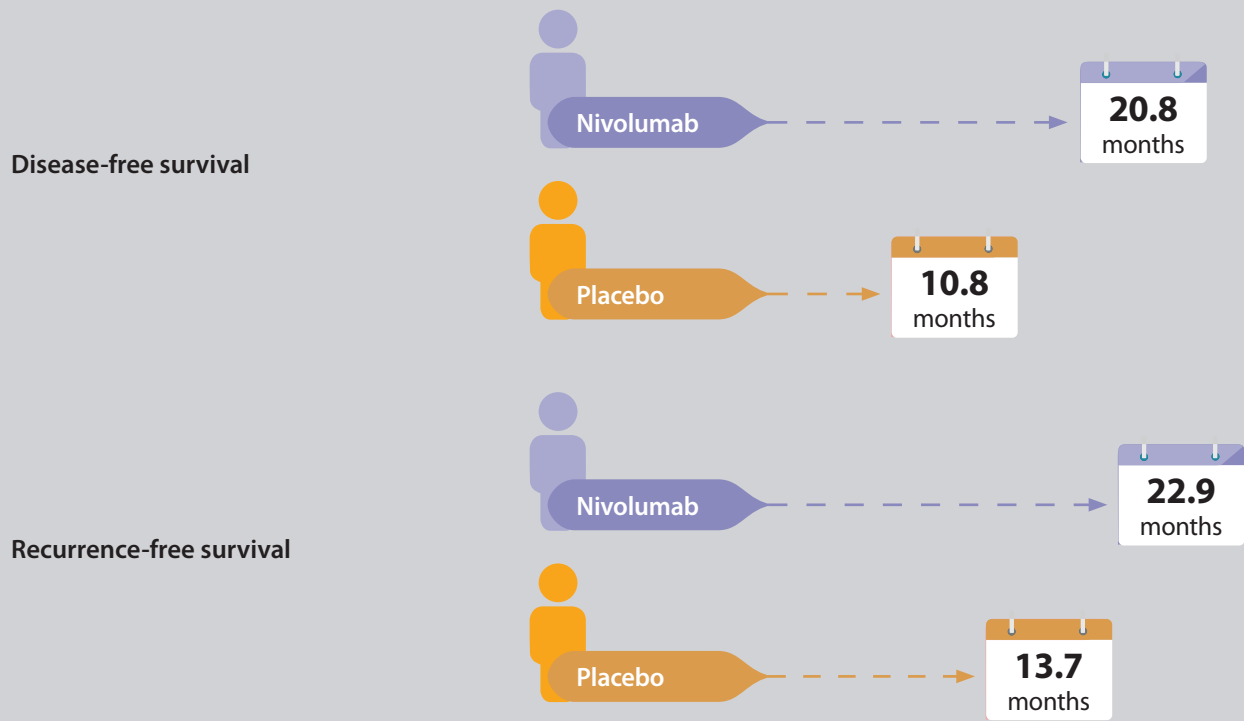
## What do the results of this study mean?

The CheckMate 274 study showed that adjuvant nivolumab treatment increased the median cancer-free time in people with muscle-invasive urothelial cancer. Compared with people who received placebo:

- People who received nivolumab had a longer median DFS.
- People who received nivolumab and had the PD-L1 protein present on their cancer cells also had longer median DFS.
- People who received nivolumab had longer median RFS.

Overall, there were no differences in the health-related quality of life between people who received nivolumab and those who received placebo. The side effects reported by people receiving nivolumab in this study were similar to side effects reported by people receiving nivolumab in other studies.

## Key findings



## Side effects

Similar with those found in previous trials of nivolumab in cancer

It is important to note that most people have only been taking part in this study for an average of 20 months, so the findings need to be further explored over a longer time. The CheckMate 274 trial is ongoing and will answer more questions, such as how long people survive after starting treatment with nivolumab and the placebo (also known as overall survival).

## Where can I find more information on the study?

- Additional information on the CheckMate 274 study is available at: <https://clinicaltrials.gov/ct2/show/NCT02632409>
- And also at: EU clinical trials register: <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2014-003626-40>

### Financial and competing interests

A full list of disclosures of the authors can be found at the end of the original article at:  
<https://www.nejm.org/doi/10.1056/NEJMoa2034442>

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