

# A plain language summary exploring a new treatment combination for untreated locally advanced or metastatic urothelial cancer: enfortumab vedotin plus pembrolizumab

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## Summary

### What is this summary about?

This summary provides the results of a study of two treatments for cancer, enfortumab vedotin and pembrolizumab, that were studied together against locally advanced or metastatic urothelial cancer (la/mUC), a cancer that occurs most commonly in the bladder.

### What were the results?

In the 45 patients studied, around 16% did have serious side effects, but most side effects were manageable. Twenty-four percent of patients, however, stopped the study treatment because of their side effects.

Within about 2 months of starting treatment, most patients' (73%) tumors were smaller and stayed smaller, on average, for more than 2 years.

### What do the results mean?

The combination of enfortumab vedotin plus pembrolizumab is a new treatment option for patients with locally advanced or metastatic urothelial cancer when they cannot receive the typical treatment, cisplatin. Advanced or metastatic urothelial cancer is a type of cancer where the cancer has already spread outside of the bladder or urinary tract.

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

- **Enfortumab vedotin:** en-FOR-too-mab veh-DOH-tin
- **Pembrolizumab:** pem-broh-LIH-zoo-mab
- **Urothelial:** yoor-oh-THEE-lee-ul
- **Cisplatin:** sis-PLA-tin
- **Chemotherapy:** KEE-moh-THAYR-uh-pee

## Who should read this article?

This article was written to help patients with locally advanced or metastatic urothelial cancer, their families, patient advocates, healthcare professionals, payers, and caregivers understand the results of this study.



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## Where can I find the original article?

The original article "Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer" was published in the *Journal of Clinical Oncology* and can be found here:

<https://ascopubs.org/doi/pdf/10.1200/JCO.22.01643>

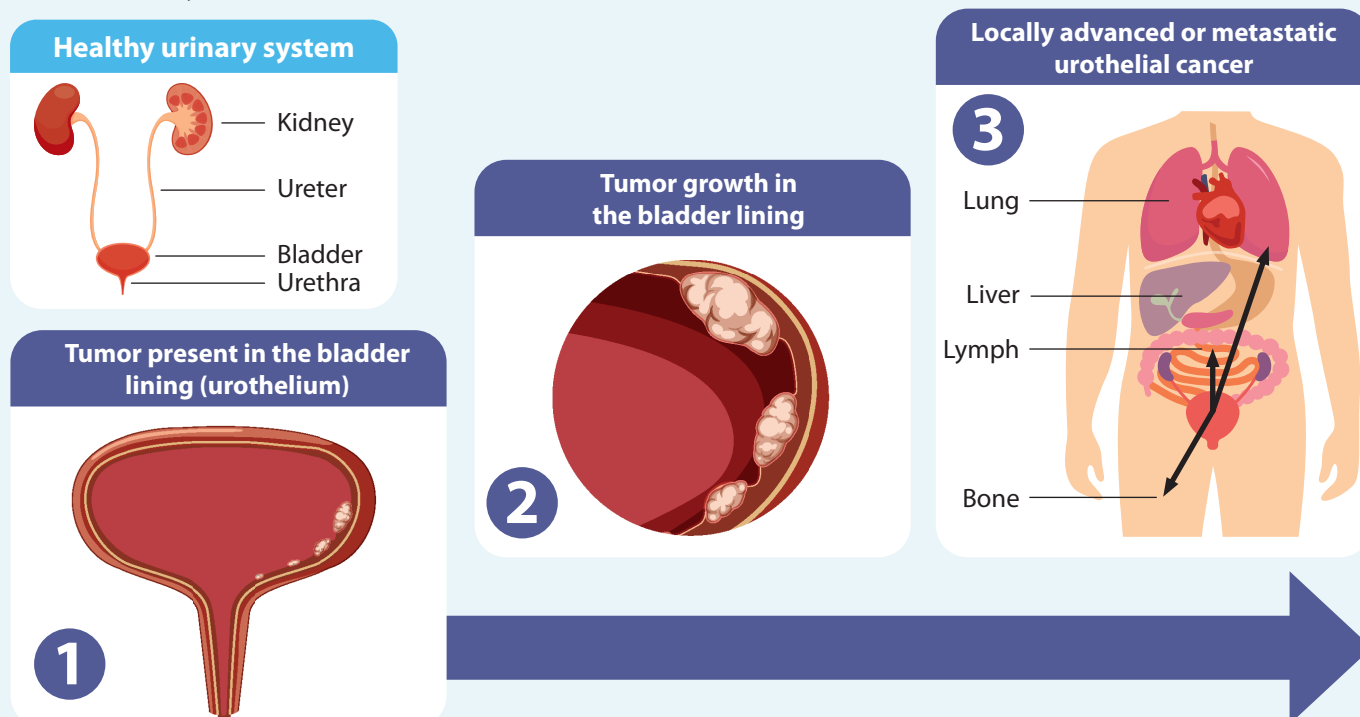
## Who sponsored this study?

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## What is locally advanced or metastatic urothelial cancer?

Locally advanced or metastatic urothelial cancer is a type of cancer that starts in the cells that make up the lining of the urinary tract. It occurs most commonly in the bladder but also may be seen in other parts of the urinary tract, such as the urethra, ureters, and kidneys. Men are about four times more likely than women to be diagnosed with urothelial cancer.

Over time, the cancer may grow through the lining and into the muscle. Surgery to remove a tumor is often needed to control the cancer when it involves the lining. If the tumor grows too deep or through the bladder lining, or into nearby organs, the doctor may not be able to fully remove the cancer with surgery, so chemotherapy (with or without the addition of radiation) may be recommended for treatment.



This cancer can spread to nearby tissues or other areas of the body, and it is then known as locally advanced or metastatic urothelial cancer. Cancer that has spread from where it started to nearby tissue or lymph nodes is called locally advanced. When cancer spreads to other areas of the body, it is called metastatic and is also known as stage 4 cancer. Prior to conducting this study, it was known that only 8 out of every 100 patients with locally advanced or metastatic urothelial cancer survive for at least 5 years after their diagnosis.

## Why was the study needed?

When patients have locally advanced or metastatic urothelial cancer, they may first be given a treatment plan that includes a chemotherapy drug called cisplatin. However, about 50% of patients cannot receive this type of chemotherapy because of its side effects. They may also have health conditions, including problems where their kidneys or heart do not function well enough to allow the use of cisplatin treatment.

Researchers are testing whether a new combination of medicines (enfortumab vedotin plus pembrolizumab) can help patients with this type of cancer who cannot receive treatments that contain cisplatin.

## What medicines were tested in the study?

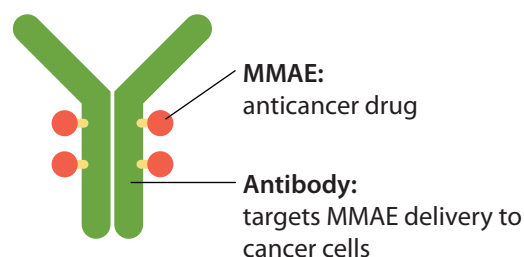
Enfortumab vedotin and pembrolizumab are approved anticancer drugs. When taken individually, each has been shown to help lengthen the time patients survive in later stages of urothelial cancer. Enfortumab vedotin and pembrolizumab, when taken together, recently received accelerated approval for the treatment of patients with locally advanced or metastatic urothelial cancer who cannot receive treatments that contain cisplatin. Accelerated approval was based, in part, on the results of this study. 'Accelerated' approval is an official process that allows a new drug to be approved before it has gone through all of the required levels of testing in people. In this study, enfortumab vedotin plus pembrolizumab were tested together as a combination treatment.

Enfortumab vedotin is a treatment made up of an anticancer drug called monomethyl auristatin E (MMAE) that is attached to an antibody. When the cancer cells die, they release molecules that alert other immune system cells to help fight cancer.

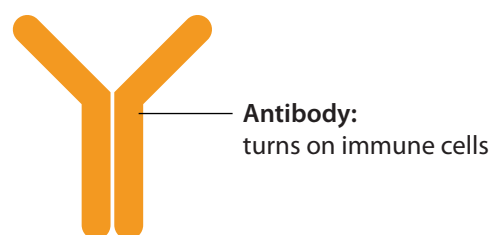
Pembrolizumab is an immunotherapy that works with your immune system to help detect and fight cancer. Immunotherapies fight cancer by allowing T cells (immune cells that help fight cancer) to find and attack cancer cells.

### Medicines tested in this study

#### Enfortumab vedotin



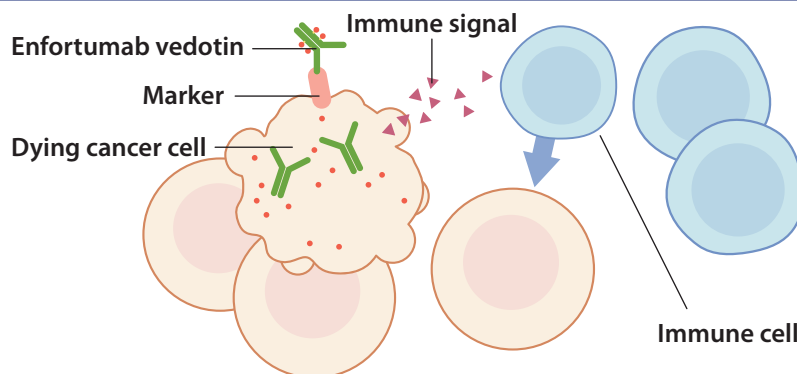
#### Pembrolizumab



### Immune response to cancer cells following treatment with enfortumab vedotin and pembrolizumab

1

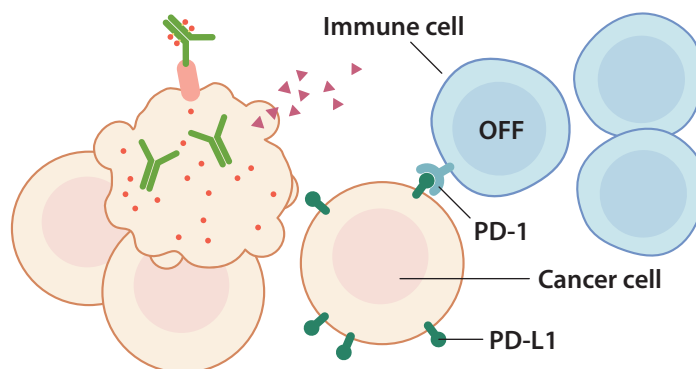
Enfortumab vedotin kills cancer cells that have a specific marker. Signals from the dying cancer cells alert immune cells to help.



## Immune response to cancer cells following treatment with enfortumab vedotin and pembrolizumab

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Some cancer cells have a protein called PD-L1 that turns off immune cells when it attaches to the receptor PD-1. After PD-L1 attaches to the PD-1 receptor, these immune cells cannot attack cancer cells.

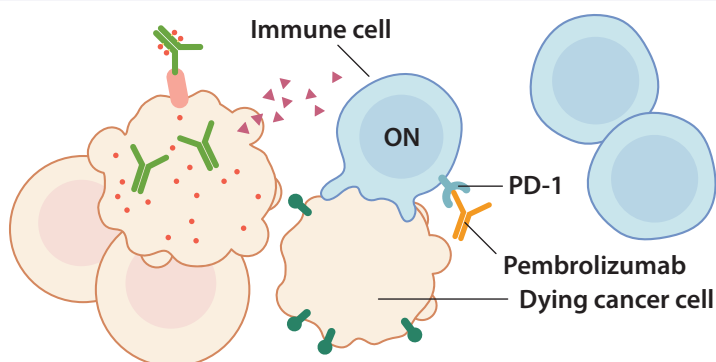


**Receptor:** a protein that resides in the cell membrane that can receive a signal.

## Immune response to cancer cells following treatment with enfortumab vedotin and pembrolizumab

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Pembrolizumab stops PD-L1 from attaching to the receptor PD-1. Immune cells are turned on. They can now help find and attack cancer cells.



Because cancer cells killed by enfortumab vedotin can send an alert that attracts immune cells and pembrolizumab can enhance the immune system's attack of the cancer cells, using the two medications together may work better and these effects may last longer.

## What questions did researchers hope to answer from this study?

In this study, researchers tested enfortumab vedotin plus pembrolizumab given together for adult patients who were not able to receive standard chemotherapy (cisplatin) for locally advanced or metastatic urothelial cancer. The researchers hoped that combining the two medications would improve outcomes for these patients.

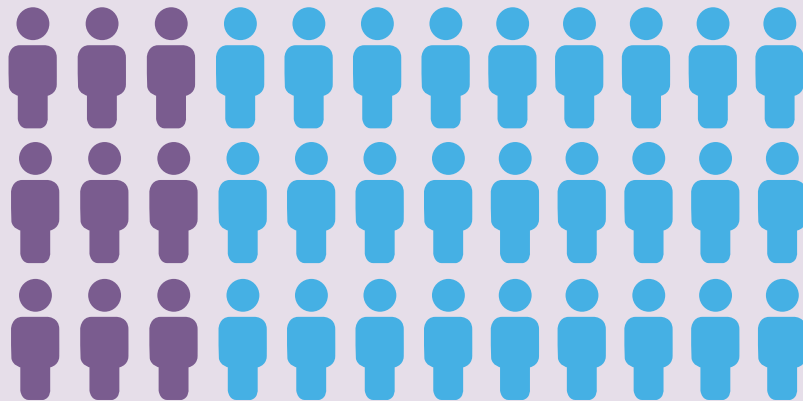
This trial provided data about how well they work when used together. This trial did not directly compare the combination with other treatments.

Who took part in this study?

This study included 45 adult patients from the United States.

Their median age was 69 years. Median is the middle number in a list, after all numbers are sorted from lowest to highest.

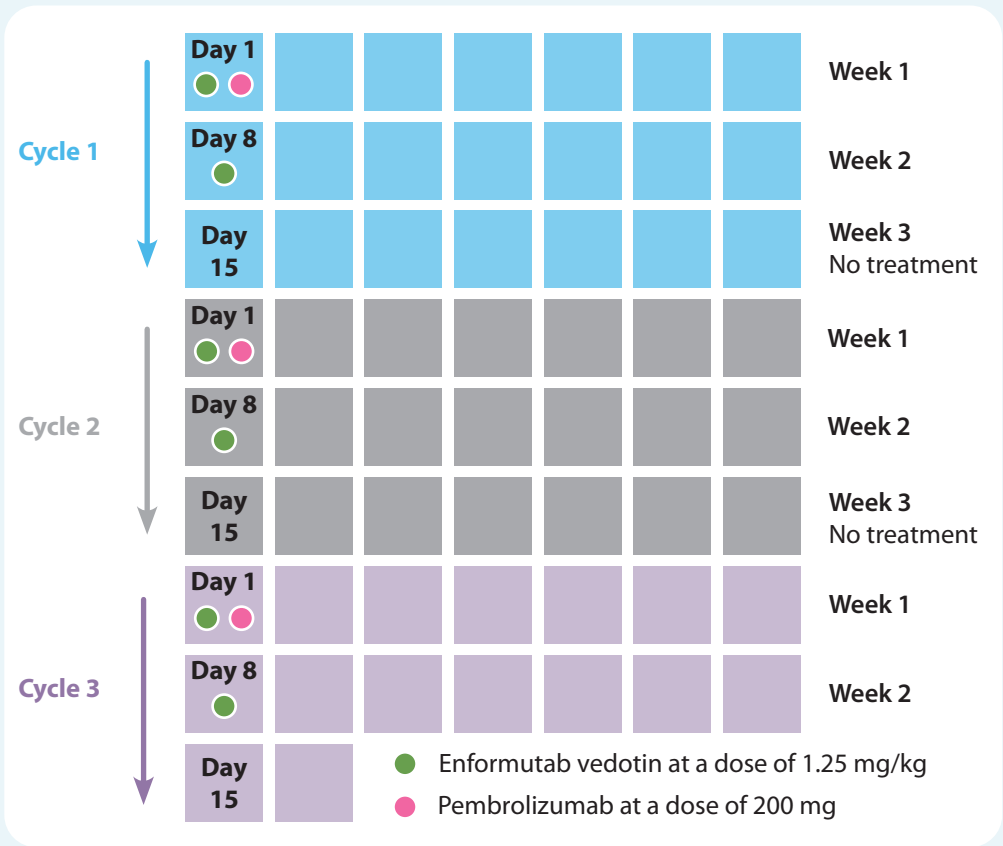
36 of these 45 patients (80%) were men. There were more men than women because men are around four times more likely than women to be diagnosed with urothelial cancer.



How was the medication given?

Enfortumab vedotin and pembrolizumab were both given by intravenous (into a vein) injection. In the first part of the study, several different doses of enfortumab vedotin were tested, from low to high, while the pembrolizumab dose remained the same. The dose of enfortumab vedotin was increased to see if the selected dose could be tolerated.

During the second part of the study, on a second set of patients, the recommended dose of enfortumab vedotin (which was considered effective and safe) in combination with pembrolizumab was given to all patients.



As shown to the left, treatments were given in 3-week cycles in an outpatient setting (where patients received the treatment and were able to go home the same day). This 3-week pattern repeated until a patient's cancer progressed (worsened) or until they had side effects that prevented them from safely receiving more study treatment.

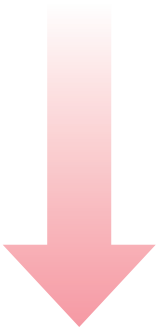
## What were the overall results of the study?

### What were the researchers trying to understand by studying this combination?

The researchers in this study were mainly focusing on the tolerability and the safety (side effects) of the enfortumab vedotin plus pembrolizumab treatment combination. A side effect is an unwanted, unpleasant, or harmful symptom a patient develops when taking a medication that may or may not be caused by the medication. It was also important for researchers to understand whether this new combination had the ability to shrink tumors and for how long tumors would stay decreased in size (efficacy).

## What were the most common side effects?

The most common side effects in patients treated with the combination of enfortumab vedotin plus pembrolizumab are shown below.



**Side effects are graded from 1 to 5**

**Grade 1** – mild, generally not bothersome

**Grade 2** – may interfere with some activities, impact quality of life

**Grade 3** – serious, interferes with the ability to do everyday activities

**Grade 4** – severe, usually requires hospitalization

**Grade 5** – fatal

**Side effects may require medical attention. A doctor should be told about any side effects, regardless of how mild they seem.**

**Common side effects of any grade occurring in at least 9 out of 45 patients**

**General symptoms**

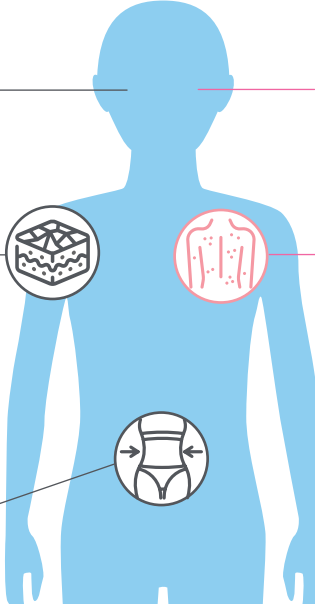
- Fatigue (tiredness) – 23 patients (51%)
- Hair loss (alopecia) – 22 patients (49%)
- Weight decreased – 11 patients (24%)

**Skin symptoms**

- Rash maculopapular (flat, red rash that is covered with small raised bumps) – 16 patients (36%)
- Itchy skin (pruritus) – 15 patients (33%)
- Dry skin – 10 patients (22%)

**Digestive symptoms**

- Diarrhea – 21 patients (47%)
- Decreased appetite – 18 patients (40%)
- Altered taste (dysgeusia) – 15 patients (33%)
- Nausea – 13 patients (29%)



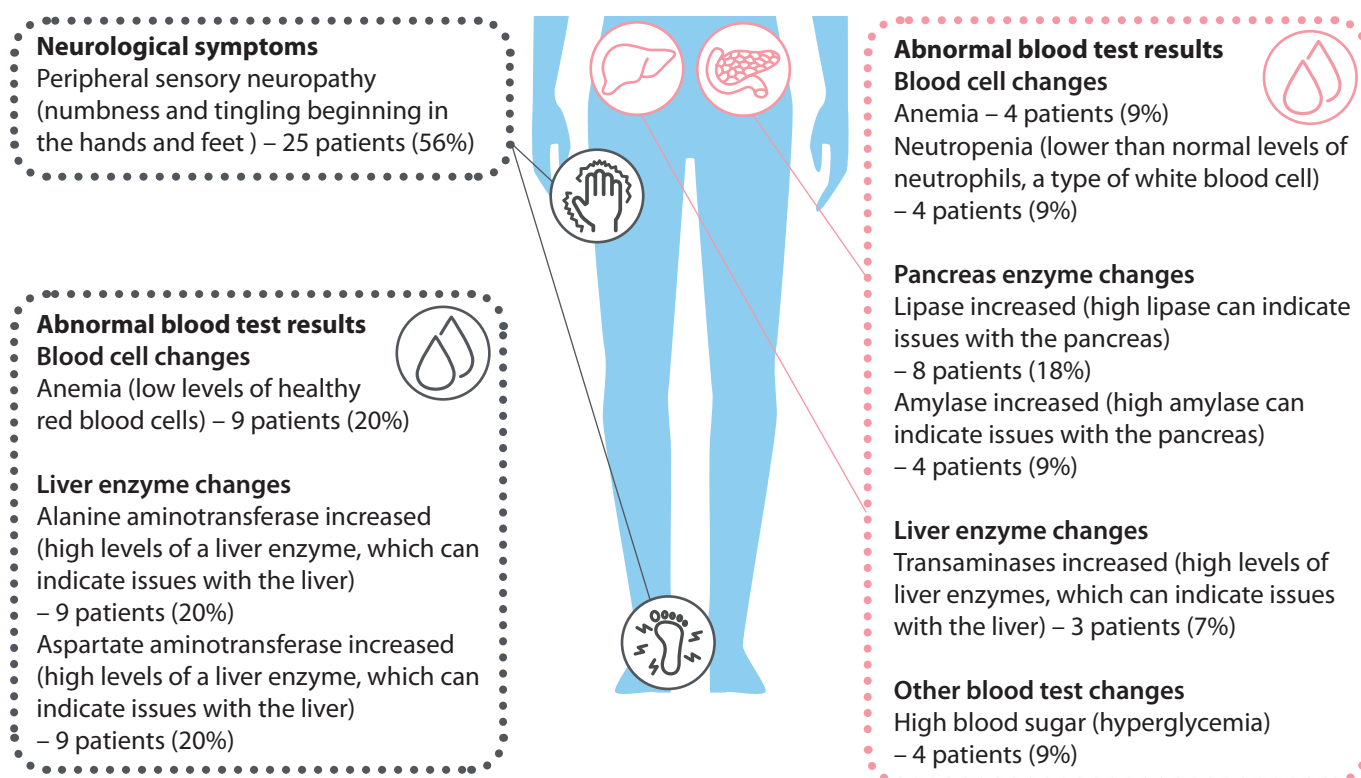
**Side effects of grade 3 or higher occurring in at least 3 out of 45 patients**

**General symptoms**

- Fatigue (tiredness) – 5 patients (11%)

**Skin symptoms**

- Rash maculopapular – 5 patients (11%)



When patients have side effects, some typically occur more often during the first weeks of treatment, while others, like neuropathy, usually occur later.

Patients should always contact their doctors or care teams as soon as possible if they suspect any side effect, including the following:

- rash
- increased and frequent urination and thirstiness
- bleeding or unexplained bruising
- unusual pain
- long-lasting diarrhea or vomiting (more than 1 day)
- tingling, numbness, or muscle weakness
- fatigue
- trouble breathing, shortness of breath, or cough
- or any symptoms they have been advised to report or are concerned about

Early recognition of signs and symptoms can help doctors promptly treat or manage side effects.

Because doctors have experience with medications like enfortumab vedotin and pembrolizumab, they have developed ways to treat and/or help reduce the side effects, which may include reducing the treatment dose or stopping treatment.

31% of patients reduced their enfortumab vedotin dose and 24% of patients stopped the treatment because of side effects.

Seven patients experienced serious side effects related to the treatment. Serious side effects are those that are life-threatening or result in hospitalization, permanent disability, or death.

One patient died because of an illness during the study. It could not be determined if the illness arose because of the treatment, the cancer, or another preexisting condition.



How well did this combination work to shrink tumors?

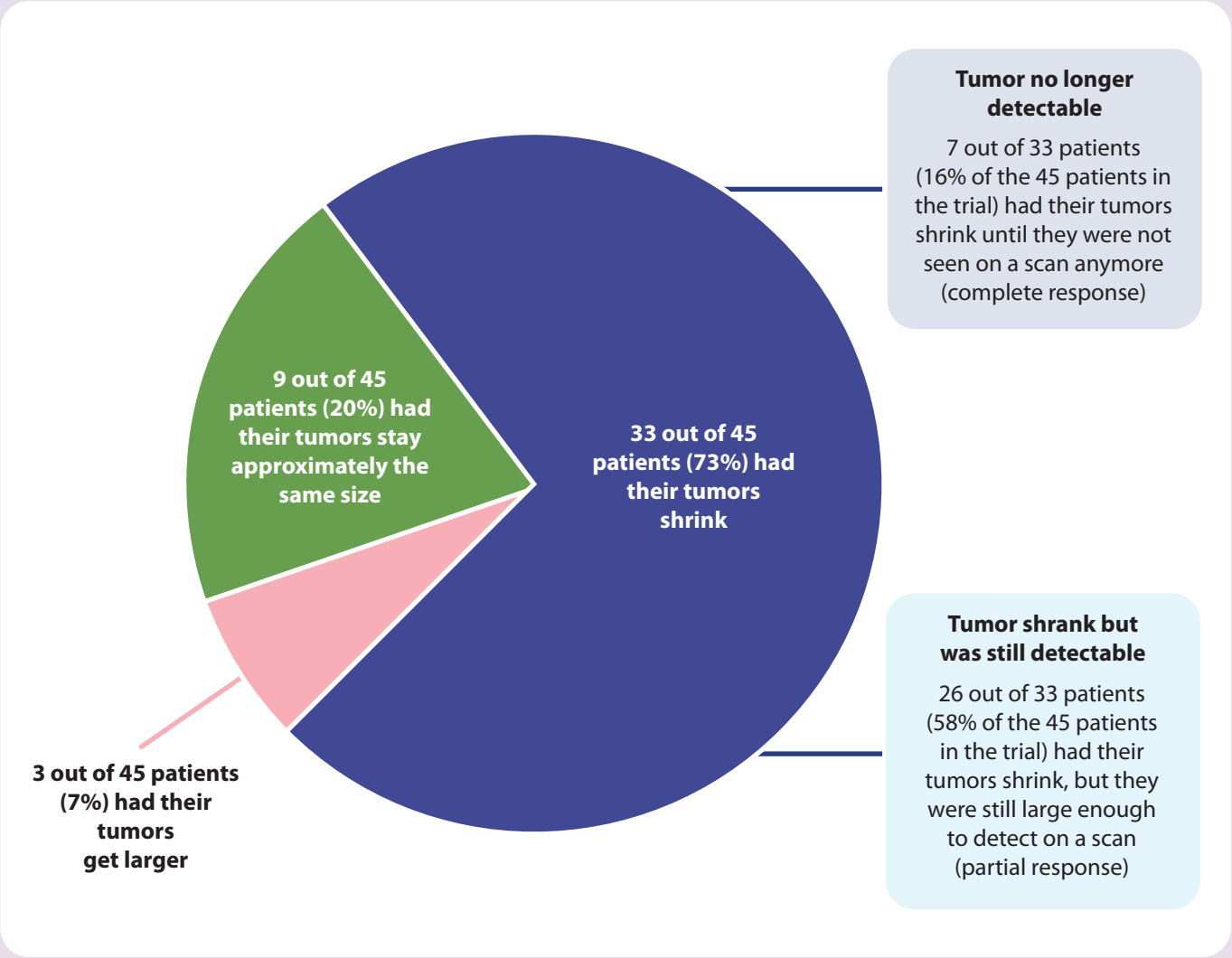
Researchers looked at how effective the combination of enfortumab vedotin plus pembrolizumab was for shrinking tumors. Tumors decreased in size in 33 (73%) patients (objective response—a response that is measured by examining scans). Of those 33 patients, 7 (16% of the 45 patients in the study) had tumors that were no longer detectable/seen on a scan (complete response).

Of the 33 patients whose tumors decreased in size, most (29 patients, 88%) learned their tumors shrank by some amount during the first scan visit, which was around 9 weeks after the first dose of treatment.

For patients whose tumors shrank because of this treatment, in more than half, the shrinkage was maintained for at least 25.6 months (more than 2 years).

More than half of the patients in the study survived for at least 26.1 months (more than 2 years) after the first dose of treatment.

More than half of the patients survived without their cancer getting worse for at least 12.3 months (this is referred to as median progression-free survival).





## What do the results of this study mean?

Enfortumab vedotin plus pembrolizumab helped shrink tumors in patients with locally advanced or metastatic urothelial cancer. Side effects patients experienced were similar to the side effects that patients experience with each medication alone. However, some skin reactions were seen more frequently with this treatment combination.

Tumors shrank for 73% of patients in this study, and for 16% of patients, tumors shrank to a size where they could no longer be seen on scans.

On average, patients survived for more than 2 years after beginning treatment.

Results are promising because about half of all patients with locally advanced or metastatic urothelial cancer cannot receive the medication cisplatin, which is used most often. Also, this cancer has a low survival rate and there are not many treatment options.

Although this is only one study, researchers believe that enfortumab vedotin plus pembrolizumab is a promising treatment for untreated locally advanced or metastatic urothelial cancer.

Because of results observed in the EV-103 study, the treatment combination of enfortumab vedotin plus pembrolizumab received accelerated approval by the U.S. Food & Drug Administration and is also being tested in more patients. In addition, a larger study is also being done to compare enfortumab vedotin plus pembrolizumab with standard chemotherapy to find out if there is improvement in survival and in the amount of time patients live without their disease worsening.

## Where can I find more information about this study?

The original article discussed in this summary is entitled “Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer” and was published in the *Journal of Clinical Oncology*. The full citation of the original article is: Hoimes CJ, Flaig TW, Milowsky MI, et al. *J. Clin. Oncol.* 2023;41(1):22–31.

You can read the original free-to-access article here: <https://ascopubs.org/doi/pdf/10.1200/JCO.22.01643>

The full name of the study is: A Study of Enfortumab Vedotin Alone or With Other Therapies for Treatment of Urothelial Cancer (EV-103)

You can read more about the study here: <https://www.clinicaltrials.gov/ct2/show/NCT03288545>

### Educational resources

You can find out more about urothelial cancer on the following websites:

- The American Cancer Society: <https://www.cancer.org/cancer/bladder-cancer.html>
- The American Bladder Cancer Society: <https://bladdercancersupport.org/>

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### Information about the study

The EV-103 trial is ongoing: study number, NCT03288545; study name, EV-103/KN-869. Sponsored by: Astellas Pharma Inc., Northbrook, IL, USA; Seagen Inc., Bothell, WA, USA; and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Trademarks are owned by or licensed to the sponsors.

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