Future Oncology

ISSN: 1479-6694 (Print) 1744-8301 (Online) Journal homepage: www.tandfonline.com/journals/ifon20

A study to learn how well enfortumab vedotin (EV) with pembrolizumab works and how safe it is in people with advanced urothelial cancer: a plain language summary of the EV-302/KEYNOTE-A39 study

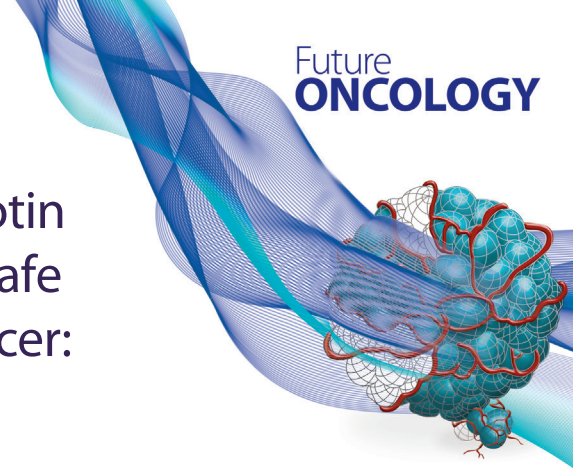
Thomas Powles, Begoña P. Valderrama, Shilpa Gupta, Jens Bedke, Eiji Kikuchi, Jean Hoffman-Censits, Gopa Iyer, Christof Vulsteke, Se Hoon Park, Sang Joon Shin, Daniel Castellano, Giuseppe Fornarini, Jian-Ri Li, Mahmut Gümüş, Nataliya Mar, Yohann Loriot, Aude Fléchon, Ignacio Duran, Alexandra Drakaki, Sujata Narayanan, Xuesong Yu, Seema Gorla, Blanca Homet Moreno & Michiel S. Van der Heijden

To cite this article: Thomas Powles, Begoña P. Valderrama, Shilpa Gupta, Jens Bedke, Eiji Kikuchi, Jean Hoffman-Censits, Gopa Iyer, Christof Vulsteke, Se Hoon Park, Sang Joon Shin, Daniel Castellano, Giuseppe Fornarini, Jian-Ri Li, Mahmut Gümüş, Nataliya Mar, Yohann Loriot, Aude Fléchon, Ignacio Duran, Alexandra Drakaki, Sujata Narayanan, Xuesong Yu, Seema Gorla, Blanca Homet Moreno & Michiel S. Van der Heijden (2025) A study to learn how well enfortumab vedotin (EV) with pembrolizumab works and how safe it is in people with advanced urothelial cancer: a plain language summary of the EV-302/KEYNOTE-A39 study, Future Oncology, 21:7, 749-764, DOI: 10.1080/14796694.2024.2415192

To link to this article: https://doi.org/10.1080/14796694.2024.2415192

Published online: 31 Jan 2025.

Plain Language Summary of Publication



Future ONCOLOGY

A study to learn how well enfortumab vedotin (EV) with pembrolizumab works and how safe it is in people with advanced urothelial cancer: a plain language summary of the EV-302/ KEYNOTE-A39 study

Thomas Powles[1], Begoña P. Valderrama[2], Shilpa Gupta[3], Jens Bedke[4], Eiji Kikuchi[5], Jean Hoffman-Censits[6], Gopa Iyer[7], Christof Vulsteke[8], Se Hoon Park[9], Sang Joon Shin[10], Daniel Castellano[11], Giuseppe Fornarini[12], Jian-Ri Li[13], Mahmut Gümüş[14], Nataliya Mar[15], Yohann Loriot[16], Aude Fléchon[17], Ignacio Duran[18], Alexandra Drakaki[19], Sujata Narayanan[20], Xuesong Yu[20], Seema Gorla[21], Blanca Homet Moreno[22] & Michiel S. Van der Heijden[23]

Full author affiliations can be found at the end of this article.

First draft submitted: 13 June 2024; Accepted for publication: 8 Oct 2024

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

The full title of the original publication in the *New England Journal of Medicine* is: "Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer". You can read the original publication for a fee at: http://doi.org/10.1056/NEJMoa2312117.

How to say (download pdf and double click sound icon to play sound)...

- **Urothelial:** Yoor-oh-THEE-lee-ul
- **Enfortumab vedotin:** En-FOR-too-mab veh-DOH-tin
- **Pembrolizumab:** Pem-broh-LIH-zoo-mab
- **Chemotherapy:** KEE-moh-THAYR-uh-pee
- **Cisplatin:** Sis-PLA-tin
- **Carboplatin:** Car-boh-PLA-tin
- **Gemcitabine:** Jem-SAI-tuh-bean
- **Urothelium:** Yoor-oh-THEE-lee-uhm
- **Ureters:** Yoor-it-ers
- **Urethra:** Yoor-eeth-ra
- **Lymph:** Limf
- **Cervix:** Sir-vix

Summary

What is this summary about?

This is a summary of the publication of the EV-302/KEYNOTE-A39 study that was published in *The New England Journal of Medicine* in March 2024. The study helped researchers learn more about a possible new treatment for advanced **urothelial cancer**. Urothelial cancer starts in the bladder or other parts of the urinary tract. **Platinum-based chemotherapy** is usually the first therapy used to treat advanced urothelial cancer, but platinum-based chemotherapy does not always work and can have many **side effects**. In this study, researchers tested how well the study drug enfortumab vedotin (EV), when given with another anticancer drug called pembrolizumab, worked compared to platinum-based chemotherapy in participants with advanced urothelial cancer.

What are the key takeaways?

Researchers found that overall, participants who received EV (enfortumab vedotin) with pembrolizumab lived about 2 times longer without their cancer growing or spreading after starting treatment compared to participants who received platinum-based chemotherapy.

Researchers also found that overall, people who received EV with pembrolizumab lived almost 2 times longer after starting treatment compared to participants who received platinum-based chemotherapy.

Almost all participants in both treatment groups had a side effect that happened during the study that was possibly related to their study treatment. About 6 in 10 participants who received EV with

Platinum-based chemotherapy: Chemotherapy that includes at least one drug that contains the element platinum, which helps kill cancer cells.

Side effect: Medical problems that may be related to a treatment or drug.

Severe side effect: A side effect that has severe symptoms, requires treatment, is life-threatening, or causes death.

Taylor & Francis
Taylor & Francis Group

pembrolizumab, and about 7 in 10 participants who received platinum-based chemotherapy, had a **severe side effect** during the study that was possibly related to their study treatment.

For participants who received EV with pembrolizumab, the most common side effect was weakness, numbness, and pain from nerve damage in the hands and feet. For participants who received platinum-based chemotherapy, the most common side effect was low numbers of red blood cells (anemia).

What were the main conclusions reported by the researchers?
Overall, researchers found that EV with pembrolizumab helped participants live longer without their cancer growing or spreading, and helped participants live longer in general, compared to platinum-based chemotherapy. Researchers believe EV with pembrolizumab should be a standard treatment option for most people who have advanced urothelial cancer that has not been treated previously with other anticancer drugs. People who receive EV with pembrolizumab should closely monitor their health and inform their healthcare team of signs of weakness, numbness, or pain in their hands and feet, or other potential side effects such as skin rashes.

What is the purpose of this plain language summary?

- The purpose of this plain language summary is to help you to understand the findings from recent research.
- Enfortumab vedotin in combination with pembrolizumab is used to treat the condition under study that is discussed in this summary. Approval varies by country; please check with your local provider for more details.
- This is the result of this one study only. Different studies may have different results. Doctors, patients, and patient advocates should make decisions together based on all available evidence.

Who is this summary for?

This summary may be helpful for people with advanced urothelial cancer, their family members, and caregivers. It may also be helpful for patient advocates and healthcare professionals. This includes those who are looking for treatment options for people with advanced urothelial cancer.

Who sponsored the study?

Astellas Pharma US, Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and Seagen, Bothell, WA, USA, which was acquired by Pfizer in December 2023, funded this study. A "subsidiary" is a company that is owned by another company.

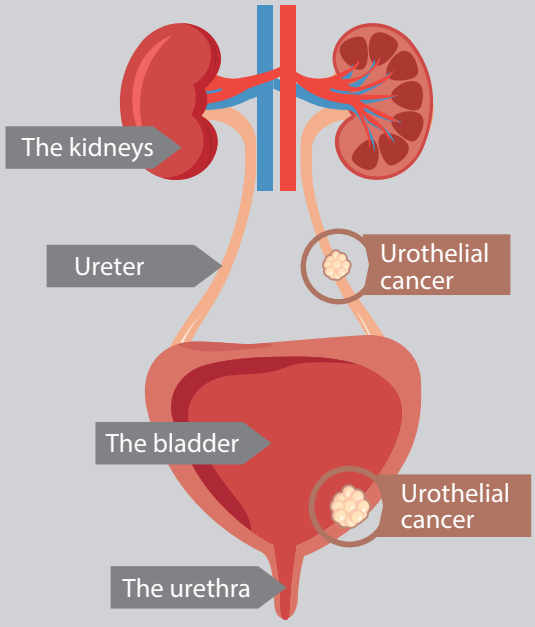
Sponsor: A company or an organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

What is advanced urothelial cancer?

The urothelium is the name for the cells that line the inside of the bladder and the urinary tract. The urinary tract filters waste from the blood and produces urine. The urinary tract starts in the kidneys, where urine is produced, and runs through the ureters to the bladder, and then to the urethra which is where the urine leaves the body.

Urothelial cancer is a type of cancer that starts in the bladder or other parts of the urinary system except for the kidney. In urothelial cancer, normal cells in the urothelium turn into cancer cells due to changes in their **DNA** called mutations. The most common location of urothelial cancer is within the bladder, which is where most of the urothelium is. But, urothelial cancer can also begin in other parts of the urinary tract.

Taylor & Francis
Taylor & Francis Group



Urothelial cancer is known as "advanced" when it has spread to the **lymph nodes** or to nearby parts of the body, such as the rectum, the prostate in males, or the uterus or cervix in females. When urothelial cancer spreads farther, such as into bones, the liver, or the lungs, it is called "metastatic". This study included people with locally advanced or metastatic urothelial cancer. In this summary, "locally advanced" and "metastatic" are together known as "advanced".

DNA: The genetic material of cells that is responsible for how the body grows and functions.

Lymph nodes: Small bean-shaped structures in different parts of the body that help with fighting infections.

How is advanced urothelial cancer usually treated?

For the past few decades, the standard first treatment for most people with advanced urothelial cancer has been platinum-based chemotherapy. Platinum-based means that the chemotherapy drugs contain the element platinum. These chemotherapy drugs are designed to kill cells that are growing and dividing quickly, like cancer cells do. But, platinum-based chemotherapy usually has many side effects and has limited benefit for many people with advanced urothelial cancer. Previous and currently ongoing studies have been conducted to test for better treatments for advanced urothelial cancer.

What were the treatments in this study?

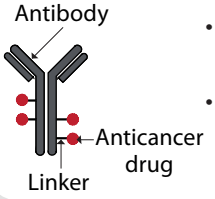
Half of the participants in this study were assigned to receive platinum-based chemotherapy, which was the standard treatment for advanced urothelial cancer at the time of the study.

Platinum-based chemotherapy

- Platinum-based chemotherapy is chemotherapy that includes at least one drug that contains the element platinum.
- Participants assigned to receive platinum-based chemotherapy in this study received gemcitabine and either cisplatin or carboplatin.

The other half of participants in this study were assigned to receive 2 drugs called EV and pembrolizumab in combination. Researchers wanted to test how well EV plus pembrolizumab worked for treating cancer compared to platinum-based chemotherapy in participants with advanced urothelial cancer.

Enfortumab vedotin



- Enfortumab vedotin (EV) is a therapy made up of 3 parts: an antibody, an anticancer drug, and a linker that connects them. This type of drug is called an **antibody-drug conjugate**.
- The antibody part of EV attaches to a protein called Nectin-4 on the surface of urothelial cancer cells. Once EV attaches to Nectin-4, it enters the cancer cell. This allows EV to deliver the anticancer drug directly to the cancer cell and kill it.

Pembrolizumab

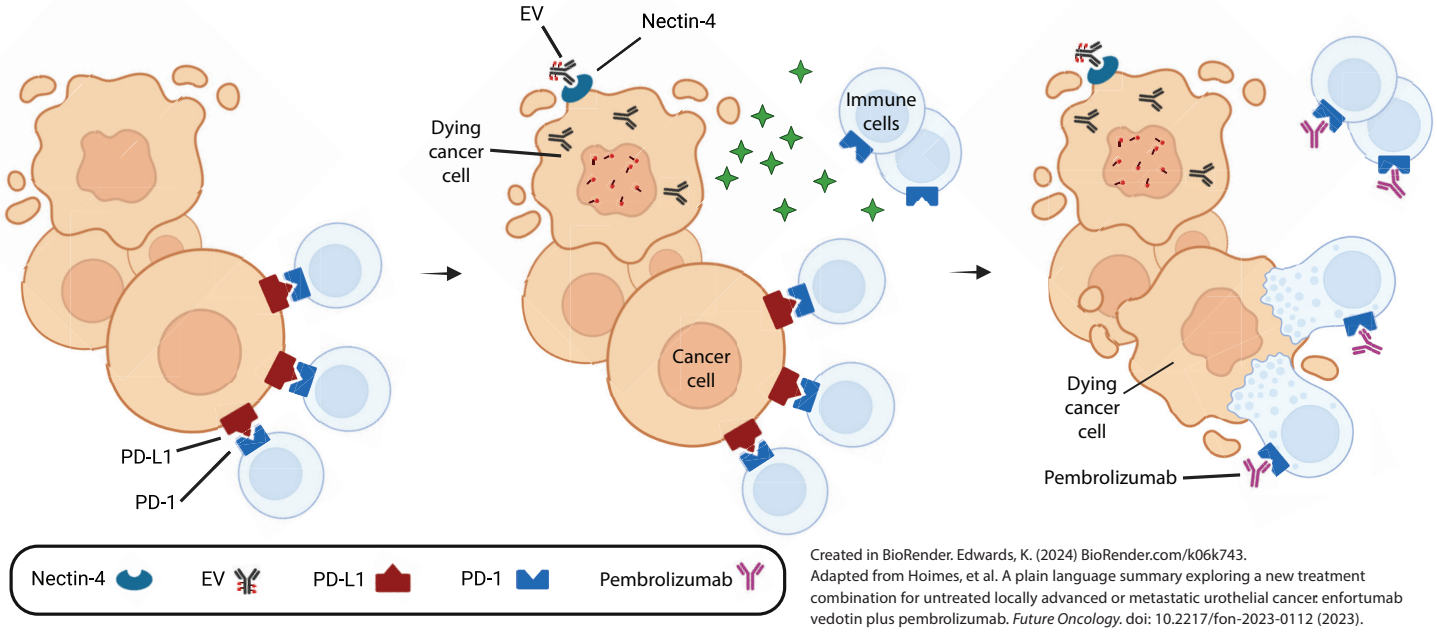
- Pembrolizumab blocks a protein called PD-1 on immune cells. **PD-1** works with another protein called PD-L1 to prevent the immune system from attacking the cancer cells. Pembrolizumab is designed to help immune cells recognize and attack cancer cells.
- Pembrolizumab is an example of a type of cancer drug called **immunotherapy**. Immunotherapy drugs help immune cells recognize and attack cancer cells.
- Pembrolizumab is a type of drug called an **antibody** that is similar in structure to the antibodies that are made by the body's immune system that find and fight off anything the body does not recognize.

How do EV and pembrolizumab work together to kill cancer cells?

1 PD-1 proteins on the immune cells attach to PD-L1 proteins on the cancer cells. This stops the immune cells from attacking the cancer cells.

2 **EV** kills cancer cells by attaching to Nectin-4 proteins and releasing the anticancer drug into the cancer cell. The dying cancer cell releases signals that tell immune cells to come and attack more cancer cells.

3 **Pembrolizumab** attaches to the PD-1 protein on immune cells, which allows them to attack and kill more cancer cells.



Created in BioRender. Edwards, K. (2024) BioRender.com/k06k743.
Adapted from Hoimes, et al. A plain language summary exploring a new treatment combination for untreated locally advanced or metastatic urothelial cancer: enfortumab vedotin plus pembrolizumab. *Future Oncology*. doi: 10.2217/fon-2023-0112 (2023).

The "signals" in Step 1 above may or may not be important for how EV and pembrolizumab work together to fight cancer. More research is needed to understand exactly how EV and pembrolizumab work together.

Taylor & Francis
Taylor & Francis Group

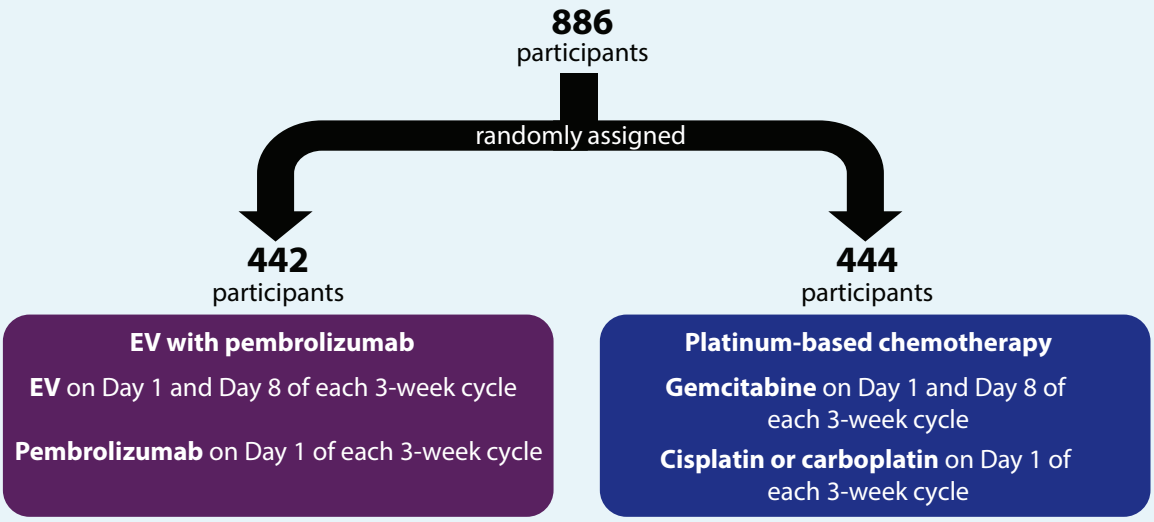
About the EV-302/KEYNOTE-A39 study

What are the goals of this study?	• To learn how well EV with pembrolizumab works for treating advanced urothelial cancer compared to platinum-based chemotherapy. • To better understand the safety of EV with pembrolizumab.
When did this study happen?	• The study started in March 2020. • Researchers looked at the results in August 2023.
How many people participated in this study?	• 886 adults in 25 countries.
What type of study was this?	• This was a Phase 3, randomized, open-label study. • In **Phase 3** studies, researchers test how well new treatments work and how safe they are compared to a standard treatment. It is usually the last step before new treatments can be approved to be received outside of clinical studies. • **Randomized** means a computer program randomly assigned the treatment each participant received. • **Open-label** means the participants, researchers, study doctors, and other study staff knew what treatment each participant received.
What primary questions did researchers want to answer in this study?	• **Did EV with pembrolizumab help participants live longer without their cancer growing or spreading, and without dying, compared to platinum-based chemotherapy?** » To answer this question, researchers tracked if participants' cancer had grown or spread based on reviews of scans of the participants' cancer throughout the study. The doctors measuring the cancer (radiologists) did not know which treatment each participant received. • **Did EV with pembrolizumab help participants live longer compared to platinum-based chemotherapy?** » To answer this question, researchers tracked how long participants lived during the study.

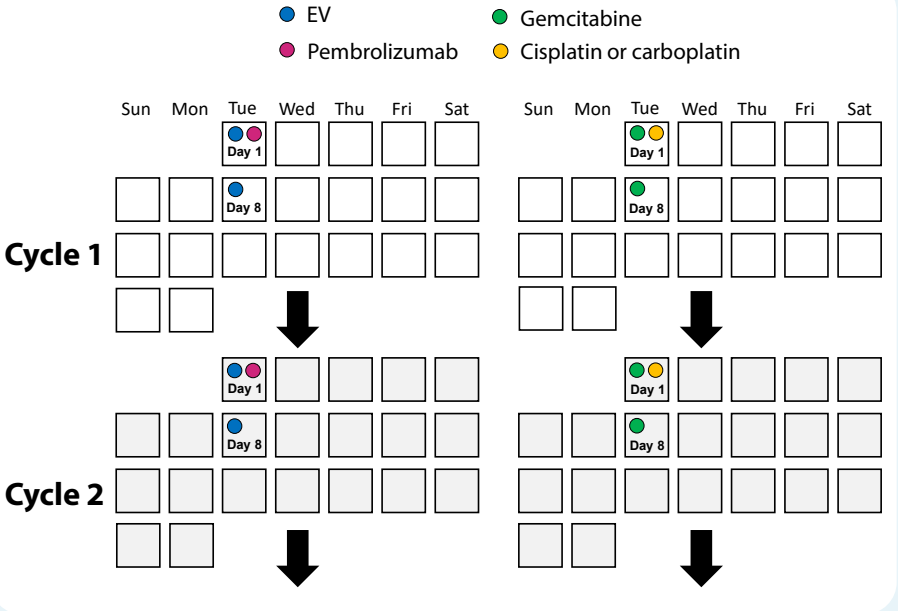
What treatments did the participants receive in the study?

Participants in this study were randomly assigned to receive either EV with pembrolizumab, or platinum-based chemotherapy. EV, pembrolizumab, and the chemotherapy drugs are all given through a needle directly into a vein (IV infusion) over a period of time.

Participants who were assigned to receive platinum-based chemotherapy received gemcitabine with either cisplatin or carboplatin. The study doctors decided whether cisplatin or carboplatin was the best option for each participant. Cisplatin was the preferred option. But, participants who had certain medical problems were not eligible to receive cisplatin, so they received carboplatin instead.



Participants received treatment in 3-week cycles.



Participants received study treatment until their cancer got worse, they had other significant medical problems, or they decided to stop treatment for another reason.

The longest amount of time participants could have received pembrolizumab was about 2 years. There was no limit on how long participants could receive EV.

The longest amount of time participants could have received platinum-based chemotherapy was 6 cycles. This decision was based on prior information from studies that showed how long platinum-based chemotherapy can be safely given. Throughout the study and after participants completed study treatment (either EV, pembrolizumab or chemotherapy), participants had their tumor status and their health monitored by study doctors until they had disease progression, died, the study closed, or they chose to stop participating in the study.

Taylor & Francis
Taylor & Francis Group

About the EV-302/KEYNOTE-A39 study participants

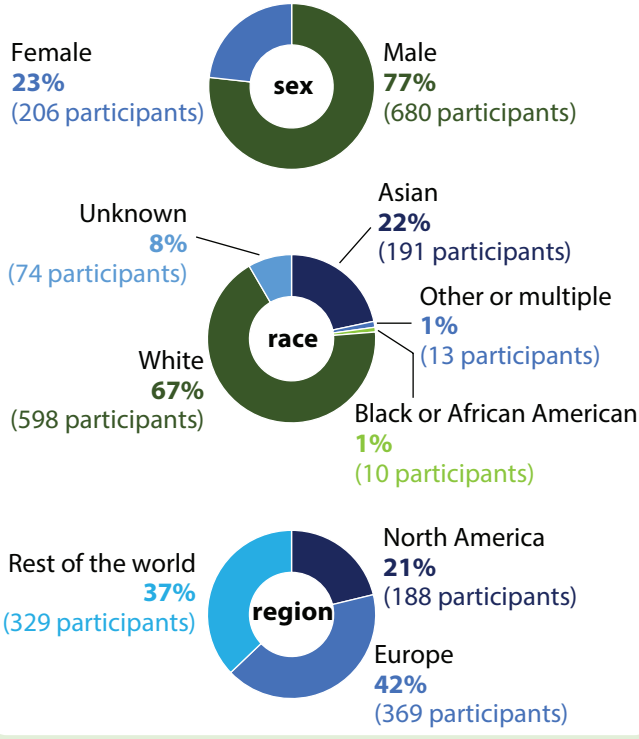
All of the participants:

- Had advanced urothelial cancer that could not be removed by surgery or had spread to other parts of the body
- Were eligible to receive platinum-based chemotherapy, EV, and pembrolizumab
- Had healthy enough kidneys
- Felt well enough to move around and care for themselves

None of the participants:

- Had received drugs to treat their advanced urothelial cancer, unless it was before or after a previous surgery to try to remove their cancer before it became advanced
- Had uncontrolled diabetes, ongoing severe nerve problems, or recent autoimmune diseases

22–91 years
age range



This study included participants from countries across the world. Most participants listed their race as either White or Asian, and the majority of participants were men. Men are more likely to have bladder cancer compared to women, so researchers in the study were expecting men to make up the majority of the participants.

What were the results from the primary questions researchers wanted to answer?

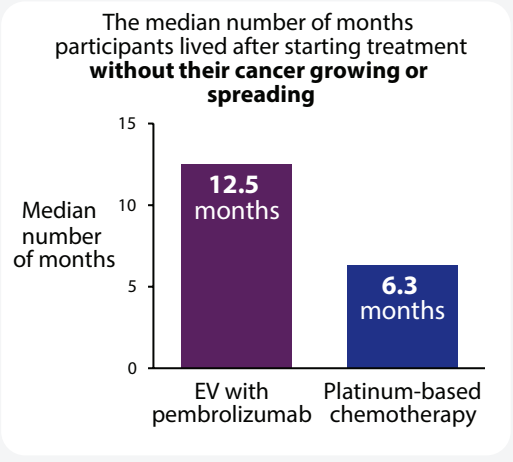
The primary questions the researchers wanted to answer in this study were:

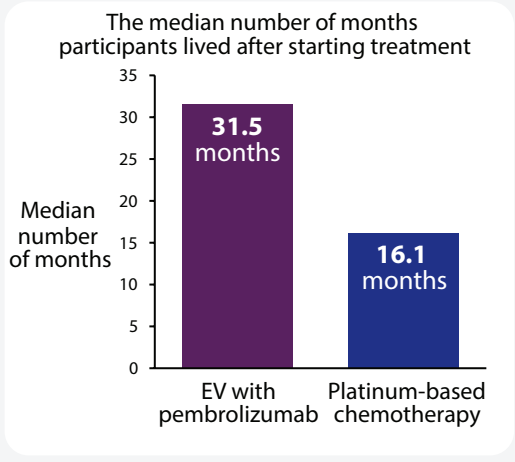
- How long did participants live without their cancer growing or spreading after starting treatment?
- How long did participants live after starting treatment?

Researchers in a central, independent committee found EV plus pembrolizumab helped participants live longer without their cancer growing or spreading compared to platinum-based chemotherapy. Researchers also found that EV plus pembrolizumab helped participants live longer compared to platinum-based chemotherapy. Results for these primary questions were calculated using a median. The median is the middle number in a set of numbers when ordered from lowest to highest. Researchers use the median because it can be a more meaningful way to summarize results compared to an average.

The researchers calculated that, overall, participants had a 55% lower risk of having their cancer grow or spread at any point after they started receiving **EV with pembrolizumab** compared with **platinum-based chemotherapy**.

The researchers calculated that, overall, participants had a 53% lower risk of dying at any point after they started receiving **EV with pembrolizumab** compared with **platinum-based chemotherapy**.





It is important to know that this study was designed to get the most accurate answers to the questions above.

Taylor & Francis
Taylor & Francis Group

What other results did researchers look at in this study?

Researchers wanted to know how many participants had their cancer shrink in response to treatment based on measurements on computed tomography (CT) or magnetic resonance imaging (MRI) scans.

To determine this, researchers used a standard set of rules called the Response Evaluation Criteria in Solid Tumors (RECIST). The RECIST system is widely used in clinical studies to consistently measure how much tumors shrink or grow in response to treatment. Using RECIST, the researchers determined if the participants' tumors had:

- Shrunk to become undetectable in scans. This is called a complete response.
- Shrunk by at least 30%. This is called a partial response.
- Shrunk by less than 30% or grown by less than 20%. This is called stable disease.
- Grown and worsened substantially. This is called progressive disease or progressing.

Researchers kept track of how many participants responded to treatment, which means that they had a complete response or a partial response. Researchers found that more participants had their cancer respond to EV plus pembrolizumab, compared to platinum-based chemotherapy. According to an independent review committee, a small number of participants did not have cancer that was measurable by CT or MRI scans when they joined the study, even though this was not consistent with the criteria for entering the study. These participants were not included in the analysis of how well participants' cancer responded to the treatments in this study.

67.7% of participants who received **EV with pembrolizumab** had their cancer respond (shrink or disappear). This was **296** out of **437** participants

44.4% of participants who received **platinum-based chemotherapy** had their cancer respond (shrink or disappear). This was **196** out of **441** participants

Complete response Partial response

The researchers also wanted to know how many participants had stable disease during the study. This meant the participants' tumors did not grow or shrink a large amount during the study.

	EV with pembrolizumab (out of 437 participants)	**Platinum-based chemotherapy** (out of 441 participants)
How many participants had **stable disease**?	**18.8%** (82 participants)	**33.8%** (149 participants)

How long did participants receive treatment in this study?

- Overall, participants received EV in this study for a median of about 7 months.
- Overall, participants received pembrolizumab in this study for a median of about 8.5 months.
- Overall, participants received platinum-based chemotherapy in this study for a median of about 4.1 months.

To learn how long it took before the participants' level of pain got worse during the study, researchers asked the participants to fill out questionnaires about their level of pain before treatment and during treatment.

Each participant answered the questionnaires based on how they felt at that time, and each participant had different experiences with pain throughout the study.

Overall, participants who received EV with pembrolizumab went longer before their pain got worse than participants who received platinum-based chemotherapy. But, the difference between the groups was too small for the researchers to be confident that the results were meaningful.

Participants who received **EV with pembrolizumab** had their pain get worse after a median of
14.2 months

Participants who received **platinum-based chemotherapy** had their pain get worse after a median of
10.0 months

Were the results similar for participants who had different levels of the PD-L1 protein in their cancer?

The researchers also compared results between participants who had high levels of the PD-L1 protein in their cancer compared to participants who had low levels of the PD-L1 protein. PD-L1 attaches to the PD-1 protein on immune cells, which prevents the immune cells from attacking the cancer. PD-1 is the protein that is targeted by pembrolizumab.

The researchers found that the results of the study were similar for participants who had high levels of PD-L1 in their cancer and participants who had low levels of PD-L1 in their cancer.

Did participants who were eligible to receive cisplatin have similar results to participants who were not eligible?

Cisplatin is a chemotherapy drug that some participants received in this study. It is commonly used to treat advanced urothelial cancer. But, cisplatin is not recommended for people with cancer who have certain other medical problems. Cisplatin may cause serious complications in these people.

In this study, if a participant was assigned to receive EV with pembrolizumab, they would not receive cisplatin even if they were eligible to receive it. Each treatment group in this study had roughly an equal number of participants who were eligible to receive cisplatin.

Researchers found similar benefits from EV with pembrolizumab compared to platinum-based chemotherapy in participants who were eligible to receive cisplatin and in participants who were not eligible to receive cisplatin. This means that the benefit of EV with pembrolizumab was not related to whether the participant was eligible to receive cisplatin.

Taylor & Francis
Taylor & Francis Group

How many participants had side effects?

In this summary, new medical problems that happened during the study that the study doctors thought were possibly related to the study treatments are called "side effects". Many clinical studies are needed for researchers to understand if a treatment causes side effects and what the side effects are.

Every time a participant had a side effect, study doctors gave it a grade of 1 to 5:

Least severe	Grade 1	Side effect with mild symptoms or no symptoms
↓	Grade 2	Side effect with some symptoms that may need minor treatment
	Grade 3	Side effect with severe symptoms and that needs treatment but is not life-threatening
	Grade 4	Side effect that is life-threatening and urgently needs to be treated
Most severe	Grade 5	Side effect that causes death

There were some participants who did not receive any treatment in this study, so their results are not shown in this section.

97% of participants who received EV with pembrolizumab had side effects, and 56% had side effects that were grade 3 or higher.

96% of participants who received platinum-based chemotherapy had side effects, and 70% had side effects that were grade 3 or higher.

4 out of 440 participants who received EV with pembrolizumab died due to side effects. These side effects were:

- Several organs in the body shutting down
- Lung disease caused by an immune system overreaction
- Severe diarrhea
- Severe ongoing weakness and fatigue

4 out of 433 participants who received platinum-based chemotherapy died due to side effects. These side effects were:

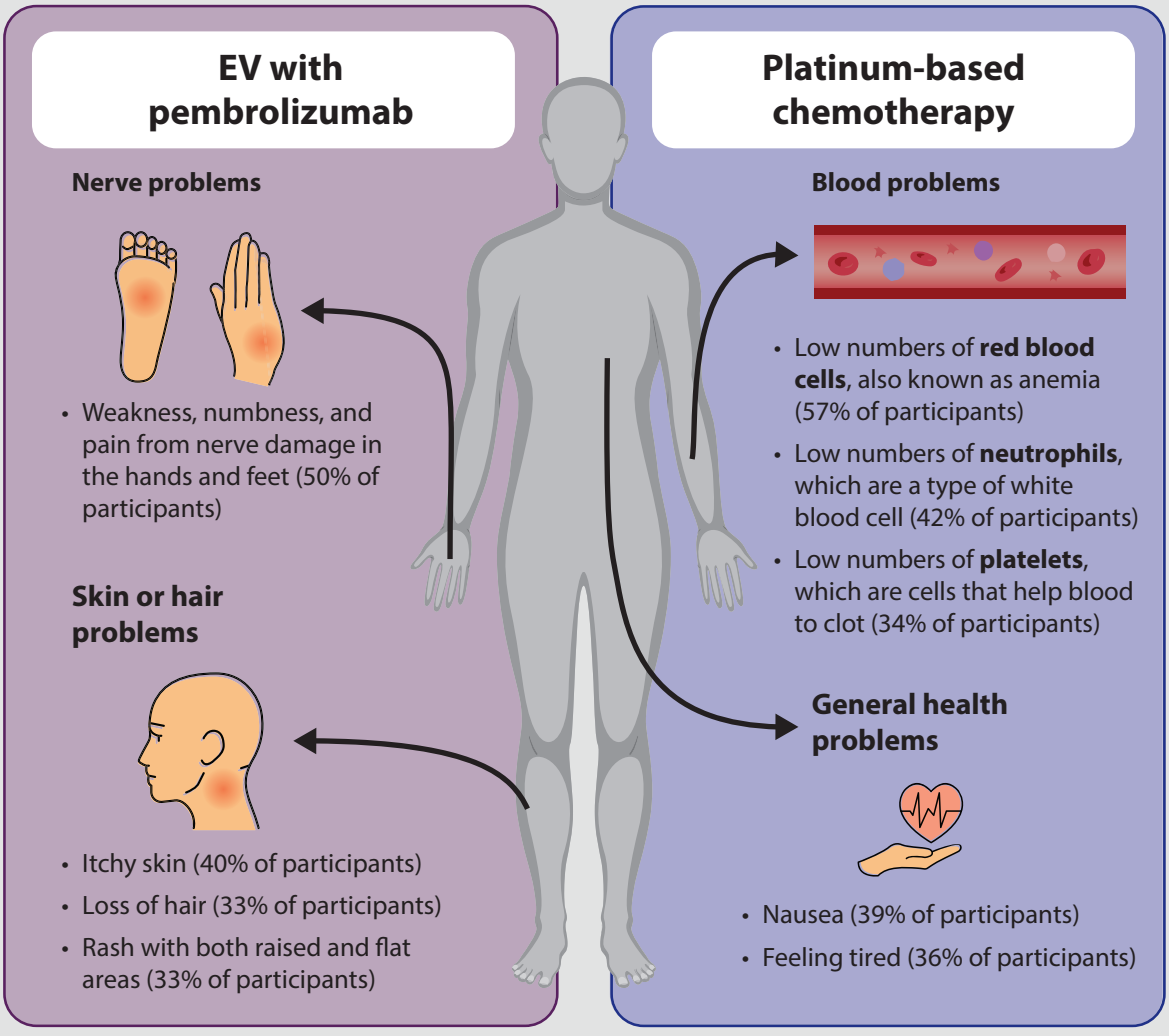
- Life-threatening reaction to an infection (sepsis)
- A fever and a low number of neutrophils, which are a type of white blood cell
- An infection due to a low number of neutrophils that can lead to organs shutting down
- Heart attack

What were the most common side effects?

The most common side effect in participants who received EV with pembrolizumab was weakness, numbness, and pain from nerve damage in the hands and feet.

The most common side effect in participants who received platinum-based chemotherapy was low numbers of red blood cells (anemia).

Other common side effects for EV with pembrolizumab included skin or hair problems, and other common side effects for platinum-based chemotherapy included general health problems.



What other side effects did the researchers think were important?

Previous research has shown that treatment with EV alone and pembrolizumab alone can be related to specific side effects. The researchers wanted to learn if participants in this clinical study also had the same side effects. These are called "side effects of special interest".

The side effects of special interest in this study included skin reactions, nerve damage in the arms and legs, eye problems, high blood sugar levels, immune system reactions to the drugs, and inflammation of organs and tissues in the body.

Similar to the other side effects, the study doctors kept track of how severe the side effects of special interest were by giving them a grade of 1 through 5. "Grade 3 or higher" means that the side effect was severe, life-threatening, or caused death.

In this study, there were some side effects of special interest that researchers thought could be due to EV based on previous research, and some that researchers thought could be due to pembrolizumab. Researchers wanted to look at how many participants in each treatment group had these side effects of special interest.

Taylor & Francis
Taylor & Francis Group

Side effects of special interest that were grade 3 or higher and have been previously associated with receiving EV alone

	EV with pembrolizumab (out of 440 participants)	Platinum-based chemotherapy (out of 433 participants)
A skin reaction	15.5% (68 participants)	0.2% (1 participant)
Nerve damage in arms and legs that causes pain, numbness, or weakness	6.8% (30 participants)	0% (0 participants)
High blood sugar levels	6.1% (27 participants)	0% (0 participants)

Side effects of special interest that were grade 3 or higher and have been previously associated with receiving pembrolizumab alone

	EV with pembrolizumab (out of 440 participants)	Platinum-based chemotherapy (out of 433 participants)
A severe skin reaction	11.8% (52 participants)	0% (0 participants)
Inflammation of the lung tissue	3.6% (16 participants)	0.2% (1 participant)
Inflammation in the liver	1.8% (8 participants)	0% (0 participants)

What do the results mean?

Based on the results of this study, researchers think that EV with pembrolizumab should be a standard treatment option for most people with advanced urothelial cancer that has not been treated previously with other anticancer drugs. People who receive EV with pembrolizumab should let their doctors know as soon as they see signs or symptoms of side effects.

Overall, the researchers found that EV with pembrolizumab helped participants live about twice as long without their cancer growing or spreading, and without dying, compared to platinum-based chemotherapy. The researchers also found EV with pembrolizumab helped participants live about twice as long during the study compared to platinum-based chemotherapy.

Overall, participants who received EV with pembrolizumab were more likely to respond to treatment than participants who received platinum-based chemotherapy.

Almost all participants in each treatment group had a side effect. About 6 in 10 participants who received EV with pembrolizumab, and about 7 in 10 participants who received platinum-based chemotherapy, had a side effect that was grade 3 or higher. For participants who received EV with pembrolizumab, the most common side effect was weakness, numbness, and pain from nerve damage in the hands and feet, and for participants who received chemotherapy it was low numbers of red blood cells (anemia).

Where can readers find more information on this clinical study?

The full title of the original publication in the *New England Journal of Medicine* is: "Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer".

You can read the original publication at: www.doi.org/10.1056/NEJMoa2312117

The full citation for the publication is: Powles T, Valderrama BP, Gupta S, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. *New England Journal of Medicine*. 2024;390(10):875-888. doi:10.1056/NEJMoa2312117

The study started in March 2020, and the researchers looked at the results in August 2023. The clinical study is currently ongoing, but it is no longer recruiting participants.

You can read more about this study on the following websites:

- Enter the study number NCT04223856 into the "Other terms" search field at www.clinicaltrials.gov.
- Enter the EudraCT number 2019-004542-15 into the search field at www.clinicaltrialsregister.eu.

If you were a study participant and have questions about the results of this study, please speak with the doctor or staff at your study center.

You can read a summary of the results of another study about EV with pembrolizumab in advanced or metastatic urothelial cancer at: https://www.tandfonline.com/doi/epdf/10.2217/fon-2023-0112?needAccess=true

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/

Acknowledgments

The authors would like to thank the clinical study participants and their family members and caregivers. They would also like to thank the staff members at the study centers who cared for the participants in the clinical study.

Funding

This manuscript was funded by Seagen Inc., which was acquired by Pfizer in December 2023, and Astellas Pharma Inc. The funder collaborated with the authors on the preparation of this plain language summary.

Declaration of interests

Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; and Seagen, Bothell, WA, USA, which was acquired by Pfizer in December 2023, funded this study. The study was designed by Astellas Pharma Inc. and Pfizer and led by Pfizer for data collection and analysis and was approved by the institutional review board at each partnering site. All authors and sponsors assisted in data interpretation, wrote the report, reviewed the

manuscript, and provided final approval to submit the manuscript for publication. Thomas Powles reports research funding to their institution from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eisai, EMD Serono, Inc., Exelixis, F. Hoffmann-La Roche, Gilead Sciences Inc., Hoffmann-La Roche Limited, Ipsen Biopharm Limited, Johnson & Johnson Health Care Systems Inc., Merck, MSD, Novartis, Pfizer, and Seattle Genetics, Inc.; consultant roles with Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eisai, EMD Serono, Inc., Exelixis, F. Hoffmann-La Roche, Gilead Sciences Inc., Incyte Corporation, Ipsen Biopharm Limited, Johnson & Johnson Health Care Systems Inc., Mashup Communications, Merck, MSD, Novartis, Pfizer, and Seattle Genetics, Inc.; paid travel from AstraZeneca, F. Hoffmann-La Roche, Gilead Sciences Inc., Ipsen Biopharm Limited, Mashup Communications, Merck, MSD, and Pfizer; strategic advisory positions with Bristol-Myers Squibb, F. Hoffmann-La Roche, and Pfizer; and is a medical oncology consultant at Queen Mary University of London. Begoña P. Valderrama reports consultant roles with Advanced Accelerator Applications, Astellas Pharma, AstraZeneca, Bayer Healthcare, Bristol-Myers Squibb, EUSA Pharma, Ipsen Biopharmaceuticals, Inc., Janssen Cilag EMEA, Merck, Novartis Pharma, and Pfizer; paid speaking engagements from Astellas Pharma, AstraZeneca, Bayer Healthcare, Bristol-Myers Squibb, EUSA Pharma, and Merck; paid travel from Astellas Pharma Bristol-Myers Squibb, F. Hoffmann-La Roche, Ipsen Biopharmaceuticals, Inc., and Pfizer; and reports consultant role for their spouse/partner from Merck Sharp and Dohme. Shilpa Gupta reports advisory board positions with Astellas Pharma US Inc., Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals Inc., Bristol-Myers Squibb Company, Eli Lilly and Company, Foundation Medicine, Inc., Genzyme Corporation, Gilead Sciences Inc., Guardant Health, Janssen Biotech, Inc., Merck Sharp and Dohme Corporation, Natera, Pfizer, and Seattle Genetics, Inc.; other consultant roles with AstraZeneca and EMD Serono, Inc.; owns stock with BioNTech and Nektar Therapeutics; paid travel from Bristol-Myers Squibb Company; paid speaking engagements with Bristol-Myers Squibb Company, Gilead Sciences Inc., Janssen Biotech, Inc., and Seattle Genetics, Inc.; research funding to their institution from Merck Sharp and Dohme Corporation and Seattle Genetics, Inc. Jens Bedke reports advisory board positions at Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Eisai, Ipsen, Janssen Pharmaceuticals, Merck Sorono, Merck Sharp and Dohme, Pfizer, and Roche; research funding to their institution from Astellas, AstraZeneca, Bristol-Myers Squibb, Eisai, Ipsen, Merch Sharp and Dohme, Nektar, Novartis, Pfizer, Roche, and Seagen; and steering committee positions from Bristol-Myers Squibb, Merck Sharp and Dohme, Pfizer, and Seagen. Eiji Kikuchi reports consultant roles with Astellas Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical Co., Ltd., Janssen Biotech, Inc., Kissei, Merck, MSD, and Pfizer; paid speaking engagements with Astellas Pharma, Bristol-Myers Squibb, Chugai Pharmaceuticals Co., Ltd., Janssen Biotech, Inc., Kissei, Merck, MSD, Nippon Kayaku, Pfizer, and Taiho Pharmaceutical. Jean Hoffman-Censits reports institutional research support from Daiichi Sankyo, EMD Serono, and Ikena Oncology, Seagen; grant support from Roche/Genentech; and consulting fees from Gilead Sciences. Gopa Iyer reports consultant roles at Bicycle Therapeutics, EMD Serono, Flare Therapeutics, Janssen Research & Development, LLC, and Loxo Oncology; research funding to their institution from Loxo Oncology, Mirati Therapeutics, Seagen Inc., and Tyra Biosciences. Christof Vulsteke reports advisory board positions with Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, F. Hoffmann-La Roche, GlaxoSmithKline, Ipsen Biopharm Limited, Janssen Pharmaceuticals, Merck Sharp and Dohme, and Pfizer; and research funding to their institution from Merck Sharp and Dohme. Se Hoon Park has no financial interests to report. Sang Joon Shin has no financial interests to report. Daniel Castellano Gauna reports scientific advisory board positions at Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, Exelixis, F. Hoffman La Roche, Ipsen Pharma SAS, Janssen Pharmaceuticals, Johnson & Johnson Health Care Systems Inc., Merck Sharp and Dohme, Novartis, Pfizer, and Seagen Inc. Giuseppe Fornarini reports interests with Amgen, Astellas Pharma, Bristol-Myers Squibb, and Eisai; a consultant position at Astellas Pharma; and paid travel from Merck and Novartis. Jian-Ri Li has no financial interests to report. Mahmut Gumus reports advisory board positions at AbbVie, Astellas Pharma, Gilead Sciences, and Novartis; research grants to their institution from Amgen and F. Hoffmann-La Roche; paid speaking engagements with AstraZeneca, Bristol-Myers Squibb, and Takeda Oncology; paid travel from F. Hoffman-La Roche and Regeneron Pharmaceuticals; professorships at Istanbul Medeniyet University and Dr. Suleyman Yalcin City Hospital; and principal investigator roles with Janssen Pharmaceuticals, Merck, Pfizer, and Regeneron Pharmaceuticals. Nataliya Mar reports paid speaking engagements with Eisai, Merck, and Seattle Genetics. Yohann Loriot reports advisory board positions with Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, F. Hoffman-La Roche, Gilead Sciences Inc., Janssen Biotech, Merck KGaA, Merck Sharp and Dohme, Pfizer, Sanofi Pasteur Inc., Seattle Genetics, and Tahio; paid travel from Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Janssen Biotech, Merck Sharp and Dohme, and Seattle Genetics; paid speaking engagements from AstraZeneca, F. Hoffmann-La Roche, Merck Sharp and Dohme, and Pfizer. Aude Flechon reports paid travel from Astellas European Foundation, Astellas Pharma, Bristol-Myers Squibb, Janssen Cilag EMEA, Merck, Merck Sharp and Dohme, Novartis, and Pfizer; and board positions at Astellas Pharma Europe, Bristol-Myers Squibb, Gilead Foundation, Janssen Cilag EMEA, Merck Sharp and Dohme, Novartis, and Pfizer. Ignacio Duran reports paid speaking engagements at Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, EUSA Pharma (US) LLC, Gilead Sciences Inc., Ipsen Pharma SAS, Johnson & Johnson, Merck, Merck Sharp and Dohme, Novartis, Pfizer, and Roche; scientific advisory board positions at Astellas Pharma, AstraZeneca, Bayer, Bristol-Myers Squibb, EUSA Pharma (US) LLC, Gilead Sciences Inc., Ipsen Pharma SAS, Johnson & Johnson, Merck, Merck Sharp and Dohme, Novartis, Pfizer, Pharmacyclics LLC, an AbbVie Company, Roche, and Seagen Inc.; principal investigator roles with Astellas Pharma, AstraZeneca, Bayer, Bicycle Therapeutics, Bristol-Myers Squibb, Eli Lilly, Gilead Sciences Inc., Ipsen Pharma SAS, Johnson & Johnson, Merck, Merck Sharp and Dohme, Pharmacyclics LLC, an AbbVie Company, Roche, and Seagen Inc.; research grants to their institution from AstraZeneca, Gilead Sciences, and Roche; paid travel from Bayer, Gilead Sciences Inc., Ipsen Pharma SAS, Johnson & Johnson, Merck, and Merck Sharp and Dohme; and a steering committee position at Gilead Sciences, Inc. Alexandra Drakaki reports advisory board positions at Astellas Pharma, AstraZeneca, Bristol Myers Squibb Company, Eli Lilly, EMD Serono, Exelixis Inc., F. Hoffmann La Roche, Infinity, Janssen Biotech, Inc., Merck Sharp & Dohme Corporation, PACT Pharma, Seagen Inc.; data and safety monitoring board position at Nektar; and paid consulting at Seagen Inc. Sujata Narayanan is employed at Pfizer Inc. Xuesong Yu is employed at Pfizer Inc. Seema Gorla is employed at Astellas Pharma Global Development. Blanca Homet Moreno is employed at Merck Sharp and Dohme and owns stock at Merck Sharp and Dohme. Michiel S. Van der Heijden reports advisory board positions paid to their institute with Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, F. Hoffmann-La Roche, Janssen Pharmaceuticals, Merck Sharp and Dohme Corporation, Pfizer, and Seagen Inc.; research funding to their institution from AstraZeneca, Bristol-Myers Squibb Company, F. Hoffmann-La Roche, and Merck Sharp and Dohme Corporation; steering committee positions paid to their institute with AstraZeneca, Bristol-Myers Squibb Company, Janssen Pharmaceuticals, Merck Sharp and Dohme Corporation, and Seagen Inc. The authors have no other competing interests, financial involvement, or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

Medical writing and editorial assistance in the development of this summary was funded by Seagen Inc., which was acquired by Pfizer in December 2023 and Astellas Pharma Inc. and provided by Samuel Entwisle, PhD, and Scott Finger of the Center for Information & Study on Clinical Research Participation (CISCRP), a non-profit organization focused on educating and informing the public about clinical research participation.

Author affiliations

[1]Saint Barts Cancer Centre, Queen Mary University of London, London, UK; [2]Hospital Universitario Virgen del Rocio, Seville, Spain; [3]Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH, USA; [4]Dept. of Urology & Transplantation Surgery, Eva Mayr-Stihl Cancer Center, Klinikum Stuttgart, Stuttgart, Baden-Württemberg, Germany; [5]St. Marianna University School of Medicine, Kawasaki, Kanagawa, Japan; [6]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [7]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [8]Integrated Cancer Center Ghent, AZ Maria Middelares, Ghent, Belgium, and Center for Oncological Research, Antwerp University, Antwerp, Belgium; [9]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [10]Severance Hospital, Yonsei University Health System, Seoul, South Korea. [11]Hospital Universitario 12 de Octubre, Madrid, Spain, [12]IRCCS Ospedale Policlinico, San Martino, Genova, Italy; [13]Taichung Veterans General Hospital, Taichung, Taiwan; [14]Istanbul Medeniyet University Goztepe Training and Research, Istanbul, Turkey; [15]University of California, Irvine Medical Center, Orange, CA, USA; [16]Institut Gustave Roussy, Université Paris-Saclay, Villejuif, France; [17]Centre Leon Berard, Lyon, France; [18]Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain; [19]University of California, Los Angeles Medical Center, Los Angeles, CA, USA; [20]Seagen Inc., Bothell, WA, USA; [21]Astellas Pharma Inc., Northbrook, IL, USA; [22]Merck & Co., Inc., Rahway, NJ, USA; [23]Netherlands Cancer Institute, Amsterdam, the Netherlands