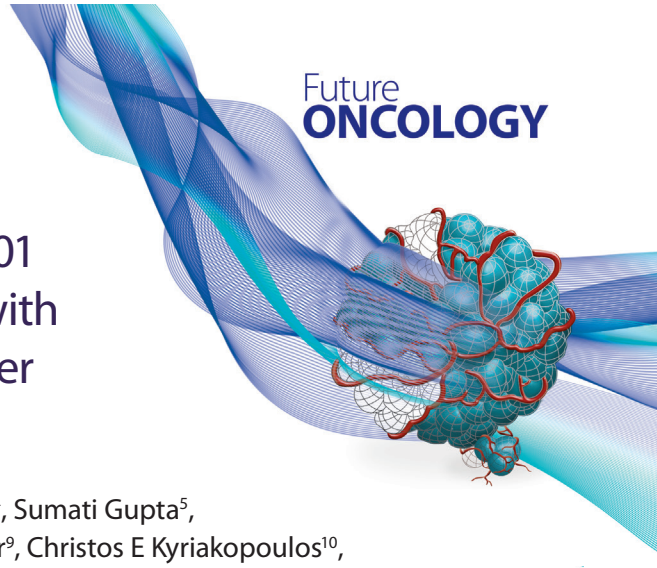
Plain Language Summary of Publication



A plain language summary of the TROPHY-U-01 study: sacituzumab govitecan use in people with locally advanced or metastatic urothelial cancer

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Summary

What is this summary about?
Sacituzumab govitecan (brand name: TRODELVY®) is a new treatment being studied for people with a type of bladder cancer, called urothelial cancer, that has progressed to a **locally advanced** or **metastatic** stage. Locally advanced and metastatic urothelial cancer are usually treated with **platinum-based chemotherapy**. Metastatic urothelial cancer is also treated with immune **checkpoint inhibitors**. There are few treatment options for people whose cancer gets worse after receiving these treatments. Sacituzumab govitecan is a suitable treatment option for most people with urothelial cancer because it aims to deliver an anti-cancer drug directly to the cancer in an attempt to limit the potential harmful side effects on healthy cells. This is a summary of a clinical study called TROPHY-U-01, focusing on the first group of participants, referred to as Cohort 1. All participants in Cohort 1 received sacituzumab govitecan.

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

- **Anemia:** ah-NEE-MEE-ah
- **Diarrhea:** dy-ah-REE-ah
- **Leukopenia:** loo-coh-PEE-nee-ah
- **Metastatic urothelial cancer:** met-ah-STA-tic yoo-ro-THEE-lee-al CAN-sir
- **Neutropenia:** noo-tro-PEE-nee-ah
- **Sacituzumab govitecan:** SAH-si-TOO-zoo-mab GOH-vih-TEE-kan
- **Antibody–drug conjugate:** AN-tee-BAH-dee–druhg KON-jih-get
- **Vinflunine:** vin-FLU-neen
- **Taxane:** TAK-sane

What are the key takeaways?
All participants received previous treatments for their metastatic urothelial cancer, including a platinum-based chemotherapy and a checkpoint inhibitor. The tumor in 31 of 113 participants became significantly smaller or could not be seen on scans after sacituzumab govitecan treatment; an effect that lasted for a **median** of 7.2 months. Half of the participants were still alive 5.4 months after starting treatment, without their tumor getting bigger or spreading further. Half of them were still alive 10.9 months after starting treatment regardless of tumor size changes. Most participants experienced **side effects**. These side effects included lower levels of certain types of blood cells, sometimes with a fever, and loose or watery stools (diarrhea). Side effects led 7 of 113 participants to stop taking sacituzumab govitecan.

What were the main conclusions reported by the researchers?
The study showed that sacituzumab govitecan had significant anti-cancer activity. Though most participants who received sacituzumab govitecan experienced side effects, these did not usually stop participants from continuing sacituzumab govitecan. Doctors can help control these side effects using treatment guidelines, but these side effects can be serious.

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Locally advanced: When the tumor grows through the bladder wall or spreads to nearby glands, known as lymph nodes.
Metastatic: When the cancer has spread beyond the bladder and nearby lymph glands to other parts of the body.
Platinum-based chemotherapy: Drugs containing platinum that are used to kill cancer cells by damaging their DNA.
Checkpoint inhibitors: Drugs, sometimes referred to as immunotherapies, which work by making the body's own immune system recognize and kill cancer cells.
Median: The middle value of a set of data, when all values are ordered from smallest to largest.
Side effect: An effect of a medicine that is beyond its desired effect. Side effects can be harmful.

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

The original article discussed in this summary is titled 'TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors'.

You can obtain a free copy of the original article here: https://ascopubs.org/doi/full/10.1200/JCO.20.03489

What is the purpose of this PLSP?

The purpose of this plain language summary is to help you to understand the findings from recent research.

Sacituzumab govitecan 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.

The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence, not on the results of a single study.

Who should read this PLSP?

This summary may be helpful for people with cancer and their caregivers, patient advocates, and health care professionals interested in new treatment options for metastatic and locally advanced urothelial cancer. It is meant to help them understand the results of the TROPHY-U-01 study.

Who sponsored the study?

This study was **sponsored** by Gilead Sciences, Inc.

Sponsor: A company or 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 metastatic urothelial cancer?

Urothelial cancer is the most common type of bladder cancer. Urothelial cancer is a disease in which cells from the bladder or other parts of the urinary tract grow out of control and form a mass, called a tumor. The tumor may grow through the bladder or urinary tract wall or spread to small nearby glands known as lymph nodes. When that happens, the disease is known as locally advanced urothelial cancer. Tumors may also spread to other parts of the body. This is called metastasis. When this happens, the cancer is then known as metastatic urothelial cancer.

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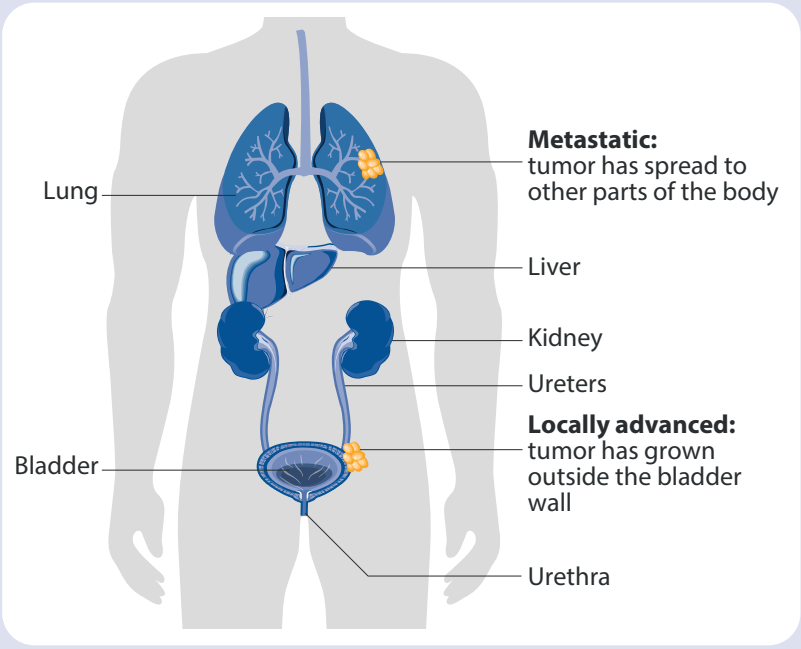
People with metastatic urothelial cancer are usually treated with platinum-based chemotherapy and another anti-cancer treatment, known as checkpoint inhibitors. Checkpoint inhibitors work by making the body's immune system recognize and kill cancer cells.

For people whose disease gets worse after platinum-based chemotherapy and checkpoint inhibitors, a few treatment options are:

- Antibody–drug conjugates, sometimes shortened to ADCs, such as enfortumab vedotin. However, enfortumab vedotin is not very suitable for people with noticeable nerve damage. More importantly, metastatic urothelial cancer still gets worse during or after treatment with enfortumab vedotin.



- Fibroblast growth factor receptor inhibitors, such as erdafitinib. This treatment has anti-cancer activity against tumors that contain specific changes in their **DNA**, called mutations or fusions. However, only around one in five people with metastatic urothelial cancer are eligible for this treatment, and, in most cases, the cancer still gets worse during or after treatment.
- **Cell division-blocking chemotherapies**, such as taxanes and vinflunine. Not many tumors respond to these treatments and people may only live about 7 to 8 months after receiving such chemotherapies. Vinflunine is only available in Europe.

The above therapies can also cause notable side effects. As such, new treatments are needed for people with metastatic urothelial cancer.

DNA: This abbreviation stands for deoxyribonucleic acid. DNA is found in every cell and controls how the cell works.
Cell division-blocking chemotherapies: These drugs disrupt the inner structure of cancer cells, stopping them from splitting into new cells. This is different from platinum-based chemotherapies, which damage the DNA of cancer cells.

What is sacituzumab govitecan?

Some cancer cells have high amounts of a protein, known as **Trop-2**, on their surface. Studies show that cancers, including urothelial cancer, with a high level of Trop-2 are more aggressive and tend to result in more severe form than cancers without high levels of Trop-2. Sacituzumab govitecan is an antibody–drug conjugate. It is designed to attach to the Trop-2 protein. Then, it aims to deliver an anti-cancer drug directly into the cancer cells. This kills the cancer cells selectively, without killing many healthy cells. This is expected to lead to fewer side effects than chemotherapy, which generally affects both cancerous and healthy cells. In April 2021, sacituzumab govitecan was approved in the United States by the FDA for use in people with locally advanced or metastatic urothelial cancer who had received previous treatments.

Trop-2: This abbreviation stands for trophoblast cell surface antigen-2. This is a protein that is present on the surface of some cancer cells.

Why did the TROPHY-U-01 study take place?

At the time of TROPHY-U-01 design, the most commonly used treatments for people with locally advanced and metastatic urothelial cancer who had received platinum-based chemotherapy and checkpoint inhibitors included a category of drugs known as taxanes and, in Europe only, vinflunine; both are chemotherapies. However, only a small proportion of locally advanced or metastatic urothelial tumors treated with these chemotherapies become significantly smaller or can no longer be seen on scans.

In a previous study, sacituzumab govitecan had an anti-cancer effect in people with various cancers, including metastatic urothelial cancer, when their cancer came back after previous treatments.

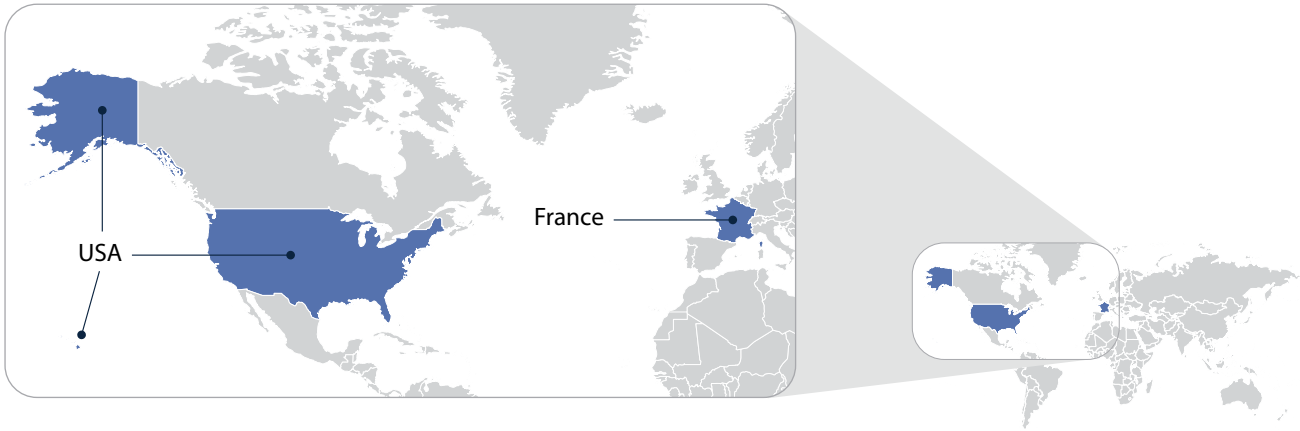
The goals of the TROPHY-U-01 study were to test how well sacituzumab govitecan worked when used for people with metastatic urothelial cancer whose cancer got worse after platinum-based chemotherapy and checkpoint inhibitor therapy, and to assess its safety.

There were six different groups of participants in the TROPHY-U-01 study. In this publication, we report on the results of the first group in this study, called Cohort 1.

Who took part in Cohort 1 of the TROPHY-U-01 study?

Participants were able to take part in this study if they:	Participants were <u>not</u> able to take part in the study if they:
✔ Had confirmed locally advanced or metastatic urothelial cancer	✖ Had Gilbert syndrome, a condition affecting the liver that can make some drugs more toxic
✔ Had received at least one platinum-based chemotherapy and a checkpoint inhibitor (and possibly other therapies) for metastatic urothelial cancer that got worse during or after such therapies	✖ Had not recovered adequately from serious side effects caused by previous treatment
✔ Had adequate organ function and blood cell counts	
✔ Had tumors that could be measured by scans	

- The average age of participants at the time they joined the study was 66 years, and 78 out of 100 participants were men (about three in every four participants).
- Two out of three participants in the study had cancer that had spread to other organs, such as the lung and liver.
- Half of the participants had received three or more prior treatments for metastatic urothelial cancer.
- Cohort 1 of the TROPHY-U-01 study included participants from the United States and France.



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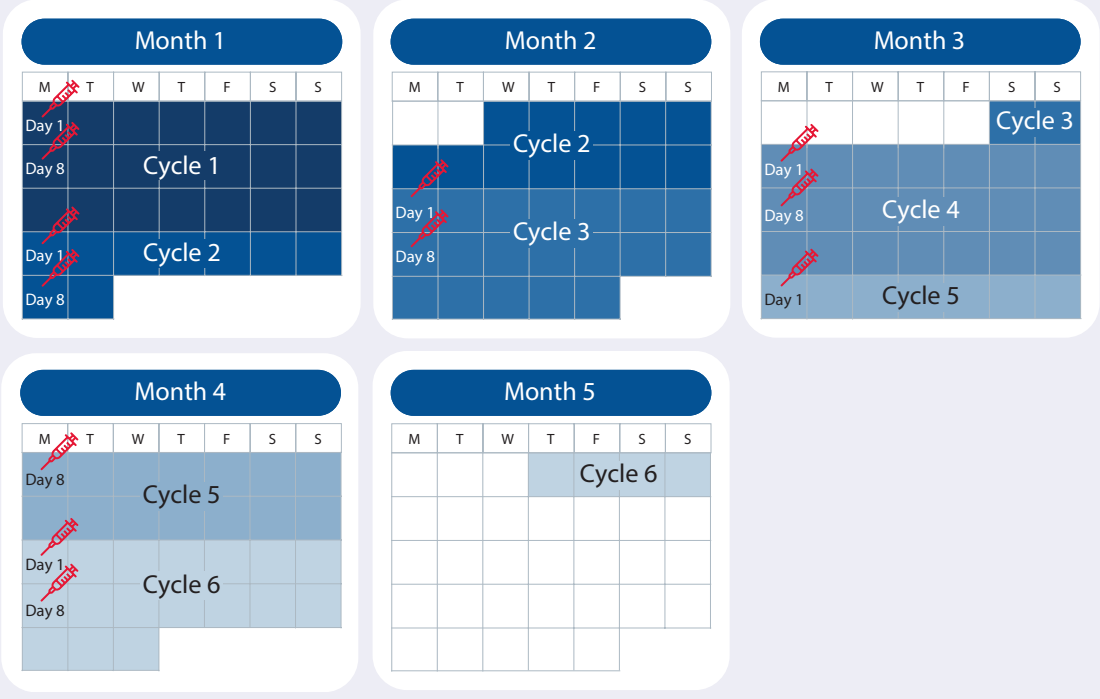
What happened in the TROPHY-U-01 study?

- The TROPHY-U-01 study began in August 2018. Cohort 1 participants could enter the trial up to November 2019.
- A total of 151 participants entered Cohort 1 of the TROPHY-U-01 study.
- Of the 151 participants in the study, 38 left the study before receiving the treatment. This left 113 participants to receive sacituzumab govitecan. Sacituzumab govitecan was given by an infusion injection into a vein (also called **intravenous** or IV treatment) on days 1 and 8 of every 21 days until one of the following occurred:
  - The tumor grew or the cancer spread further
  - Side effects were not acceptable to the participant
  - Treatment was delayed for more than 5 weeks (or for more than 3 weeks during the first 6 cycles)
  - Treatment was stopped voluntarily
  - The participant died, or no longer agreed to participate
  - The study ended
- The treatments lasted for a median of 6 cycles, or 11 doses.

Intravenous: When a needle is inserted directly into a vein and the treatment is delivered straight into the bloodstream via a tube.

Sacituzumab govitecan injection schedule:



What were the key questions answered in Cohort 1 of the TROPHY-U-01 study?

The key questions the TROPHY-U-01 study researchers asked are as follows:

- What was the proportion of participants whose cancer either cannot be seen on scans (known as a complete response) or whose tumors became significantly smaller (called a partial response)? This was the main question that the study was designed to answer.
- For participants whose tumor got smaller with sacituzumab govitecan, how long did this last? This is called duration of response.
- How long did participants receiving sacituzumab govitecan survive without their tumor getting bigger or spreading further? This is called progression-free survival.
- How long did participants who received sacituzumab govitecan live? This is called overall survival.
- Did participants receiving sacituzumab govitecan have any serious side effects caused by the treatment?

What were the overall results of Cohort 1 of the TROPHY-U-01 study?

In August 2021, the TROPHY-U-01 study group published their analysis of the study results from Cohort 1 in the *Journal of Clinical Oncology*.

1 Changes in tumor (main question)

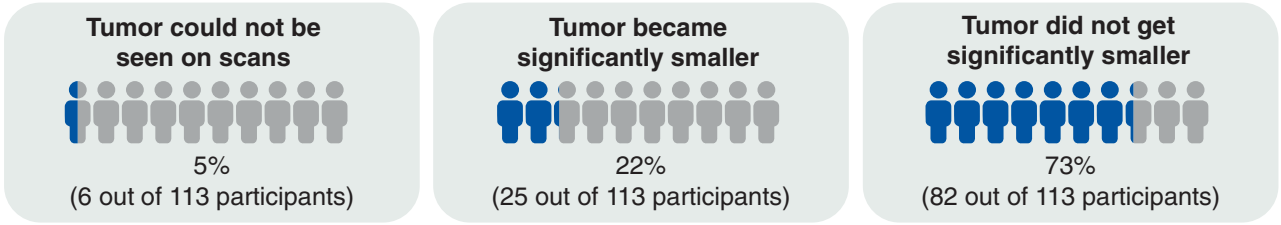
The researchers reported most results in terms of the median length of time. The median is the middle value of a set of data, when all values are ordered from smallest to largest.

What proportion of tumors became significantly smaller?

For 31 out of 113 participants, the tumors either became significantly smaller (known as partial response) or could not be seen on scans at all (known as complete response): 25 had a partial response and 6 had a complete response.

Among the 31 participants whose tumors either became smaller or could no longer be seen on scans, this was detected at the first scan for half of these participants. The first scan took place 6 weeks (approximately 1.6 months) after starting sacituzumab govitecan treatment.

Tumor response to sacituzumab govitecan treatment



For participants whose tumor got significantly smaller, how long did it remain smaller?

Tumors remained significantly smaller or could not be seen for a median time of 7.2 months.

2 Survival

How long did participants live without their tumor getting bigger or spreading further?

Half of the participants who received sacituzumab govitecan were still alive 5.4 months after starting treatment, without their tumor getting bigger or spreading further.

How long did participants survive?

Half of the participants who received sacituzumab govitecan were still alive after 10.9 months from the start of treatment.

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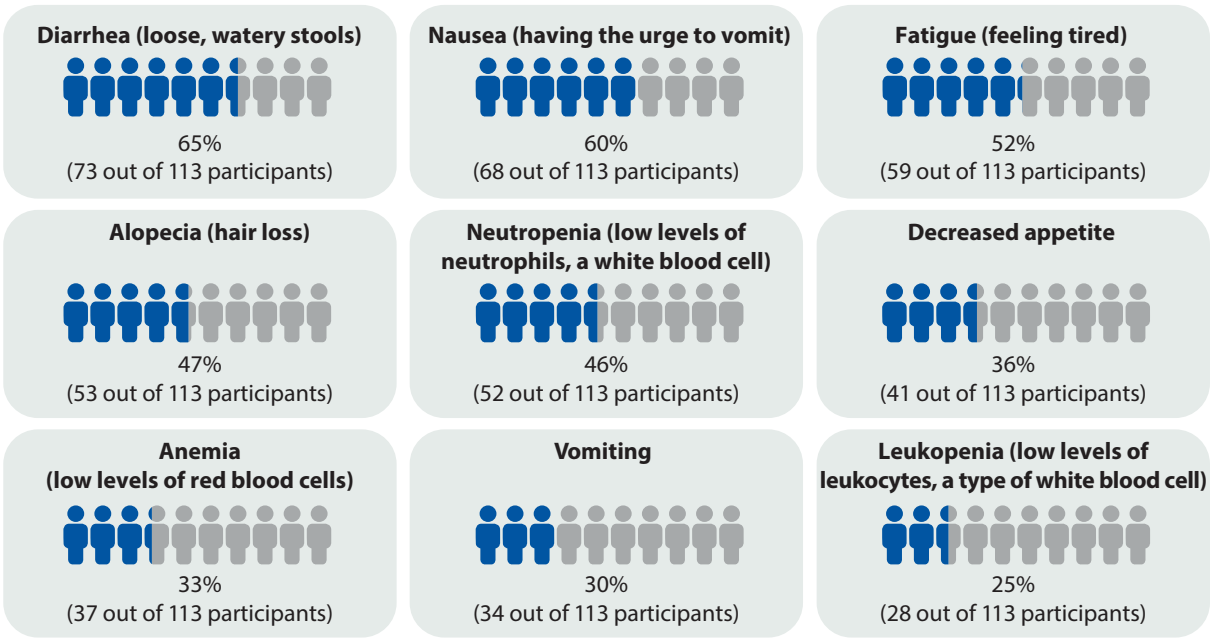
3 Safety

107 out of 113 participants experienced a side effect. Side effects were managed according to medical guidelines in most cases. In some cases, participants had a side effect that required a dose reduction, temporary stop, or permanent stop of sacituzumab govitecan treatment. These side effects are shown in the graphs below

What were the most common side effects?

All side effects that occurred in more than 20 out of 100 participants are shown below and labeled as most common side effects.

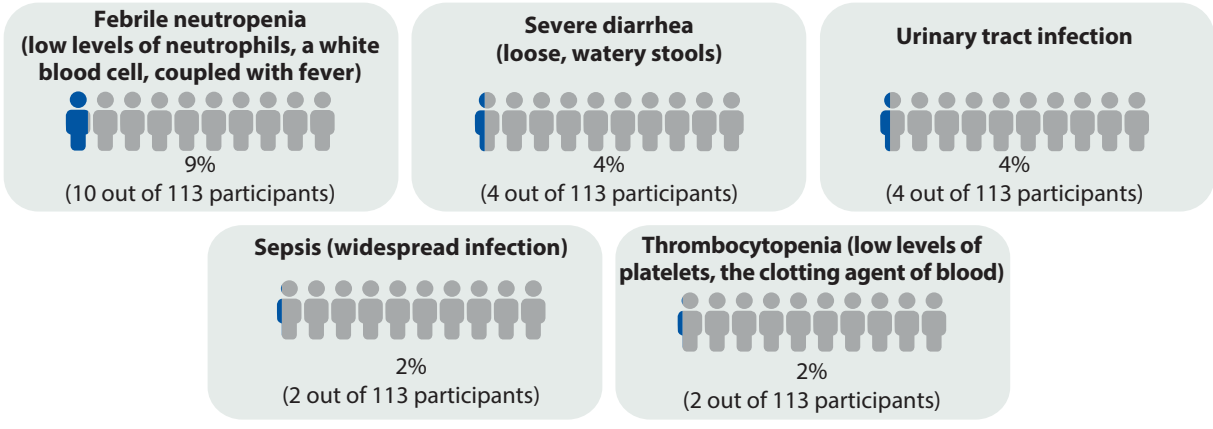
Most common side effects among 113 participants receiving sacituzumab govitecan



What were the most concerning side effects?

The most severe, life-threatening or concerning side effects are shown below and occurred in a small number of participants.

Most severe/life-threatening side effects among 113 participants receiving sacituzumab govitecan

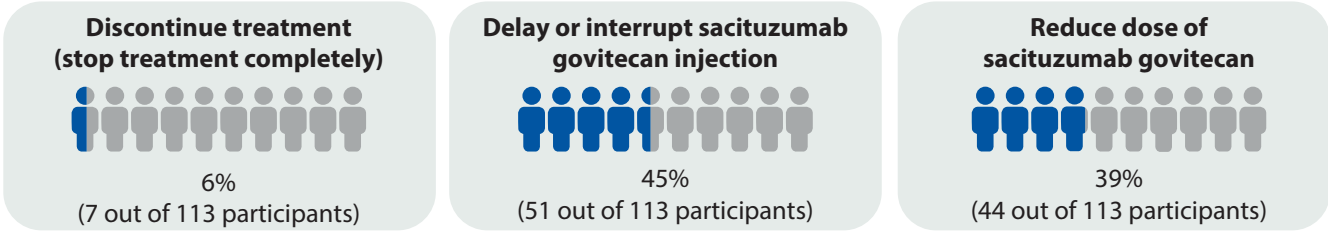


How were side effects managed in participants?

Side effects were mostly treated with over-the-counter medications, including anti-diarrhea and/or anti-sickness medicines and hydration. Additionally, substances that stimulate the bone marrow to make white blood cells were given to a number of participants during treatment to manage neutropenia. These substances are called growth factors for white blood cells.

A subset of participants (about 1 in 10) did need to modify the dose and/or stop taking sacituzumab govitecan completely to manage their side effects.

Management of side effects



Did any participants die because of sacituzumab govitecan treatment?

One of the 113 participants in the study developed neutropenia, which is a low level of white blood cells that help to fight infections. Subsequently, the person developed a widespread severe infection, called sepsis, and died. The neutropenia was thought to be caused by sacituzumab govitecan.

What do the Cohort 1 results of the TROPHY-U-01 study mean?

Results from this study showed that sacituzumab govitecan has significant anti-cancer activity in participants with urothelial cancer that has invaded the bladder wall or spread to other areas of the body, whose cancer got worse after being treated with platinum-based chemotherapy, a checkpoint inhibitor, and possibly many other therapies. While Cohort 1 of the TROPHY-U-01 was not designed to compare sacituzumab govitecan with another treatment, looking indirectly at other studies on the **efficacy** of cell division-blocking chemotherapies (for example, taxanes or vinflunine) in this population, sacituzumab govitecan appears to provide better results. However, a direct comparison is ongoing in a study called TROPiCS-04.

Although most participants who received sacituzumab govitecan experienced side effects, these did not usually stop participants from continuing sacituzumab govitecan. In addition, the side effects were expected, meaning doctors could manage these by following guidelines. A number of participants were given growth factor drugs for white blood cells to prevent severe side effects.

Efficacy: How well the treatment works.

Significance

Sacituzumab govitecan is an effective, feasible, and generally safe treatment for people with metastatic urothelial cancer. The promising Cohort 1 results of the TROPHY-U-01 study helped speed up FDA approval in the United States of sacituzumab govitecan for the treatment of people with metastatic urothelial cancer previously treated with chemotherapy and a checkpoint inhibitor.

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What does the TROPHY-U-01 study mean for the patient community?

"Bladder cancer in 2024 remains an understudied, underfunded, and deadly disease. Urothelial cancer is the most common form of bladder cancer. About one in four urothelial cancer survivors will have an initial diagnosis indicating that the cancer has grown beyond the bladder (advanced urothelial cancer) or to other parts of the body (metastatic urothelial cancer). Clinical studies remain the best way to improve the results of urothelial cancer treatments. The TROPHY-U-01 clinical study suggests sacituzumab govitecan may be a promising treatment for people with these diagnoses who have previously received the usual treatment with platinum-based chemotherapy and a checkpoint inhibitor. Additional studies with a larger patient population will hopefully validate the promise of sacituzumab govitecan."

– Rick Bangs, Patient Advocate

Ongoing research

Cohort 1 of the TROPHY-U-01 study did not compare sacituzumab govitecan with another treatment. Because of this, an ongoing study is testing the safety and how well sacituzumab govitecan works compared with cell division-blocking chemotherapies (taxane or vinflunine) in a larger number of participants with metastatic urothelial cancer (TROPiCS-04; ClinicalTrials.gov identifier: NCT04527991; https://clinicaltrials.gov/study/NCT04527991).

The TROPHY-U-01 study continues to look at the role of sacituzumab govitecan in metastatic urothelial cancer in different cohorts. The information in this article comes from the first group, Cohort 1.

In Cohort 2, sacituzumab govitecan was studied in participants with metastatic urothelial cancer that had gotten worse after a checkpoint inhibitor. In this cohort, the participants could not receive chemotherapy using cisplatin, a kind of platinum-based drug, for medical reasons.

In Cohort 3, sacituzumab govitecan was studied in combination with a checkpoint inhibitor called pembrolizumab. This combination was investigated in participants with metastatic urothelial cancer that got worse after platinum-based chemotherapy, but who had not received a checkpoint inhibitor. (Results from Cohort 3 have been published. You can obtain a free copy of this article here: https://ascopubs.org/doi/10.1200/JCO.22.02835).

There are three more groups studying sacituzumab govitecan with other combinations as the first treatment for people with metastatic urothelial cancer. Cohort 6 is currently signing up participants (ClinicalTrials.gov identifier: NCT03547973, link in the section below).

Where can readers find more information on the TROPHY-U-01 study?

The original Cohort 1 TROPHY-U-01 article is titled 'TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors'.

You can obtain a free copy of the original article here: https://ascopubs.org/doi/full/10.1200/JCO.20.03489

The full citation for the original publication is: Tagawa ST, Balar AV, Petrylak DP, et al. TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. J Clin Oncol. 2021;39(22):2474–2485. doi: 10.1200/JCO.20.03489.

The study started in August 2018 and recruitment ended in November 2019.
You can read more about the TROPHY-U-01 study at ClinicalTrials.gov: https://www.clinicaltrials.gov/study/NCT03547973

You can read more about sacituzumab govitecan here:
European Medicines Agency (https://www.ema.europa.eu/en/medicines): type "sacituzumab govitecan" into the search bar to find the public assessment report or go to: https://www.ema.europa.eu/en/medicines/human/EPAR/trodelvy

If you participated in the TROPHY-U-01 study and have questions about the results presented in this summary, or sacituzumab govitecan (brand name TRODELVY®), please speak with the physician or other staff at the study site in which you participated.

Educational resources
Read more about bladder cancer on the Cancer.Net website at:
https://www.cancer.net/cancer-types/bladder-cancer

You can also read more in the National Comprehensive Cancer Network® patient guidelines for bladder cancer:
https://www.nccn.org/patients/guidelines/content/PDF/bladder-patient.pdf

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Institutional review board: A group that has been asked to review and monitor medical research.
Site: Where trial participants can take part in a clinical trial.

Competing interests disclosure

Y Loriot: Honoraria: Sanofi, Pfizer. Consulting or Advisory Role: Janssen, Astellas Pharma, Roche, AstraZeneca, MSD Oncology, MSD Oncology, Seattle Genetics, Bristol Myers Squibb, Immunomedics, Taiho Pharmaceutical. Research Funding: Sanofi, Janssen Oncology, MSD Oncology, AstraZeneca, Clovis Oncology, Exelixis, Boehringer Ingelheim, Incyte, Pfizer, Oncogenex, Medivation, CureVac, Nektar. Travel, Accommodations, Expenses: Astellas Pharma, Janssen Oncology, Roche, MSD Oncology, AstraZeneca, Seattle Genetics. A Rezazadeh: Stock and Other Ownership Interests: ECOM Medical. Consulting or Advisory Role: Exelixis, AstraZeneca, Bayer, Pfizer, Novartis, Genentech, Bristol Myers Squibb, EMD Serono, Immunomedics, Gilead Sciences. Speakers' Bureau: Janssen, Astellas Medivation, Pfizer, Novartis, Sanofi, Genentech/Roche, Eisai, AstraZeneca, Bristol Myers Squibb, Amgen, Exelixis, EMD Serono, Merck, Seattle Genetics/Astellas, Myovant Sciences, Gilead Sciences, AVEO. Research Funding: Genentech, Exelixis, Janssen, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Macrogenics, Astellas Pharma, BeyondSpring Pharmaceuticals, BioClin Therapeutics, Clovis Oncology, Bavarian Nordic, Seattle Genetics, Immunomedics, Epizyme. Travel, Accommodations, Expenses: Genentech, Prometheus, Astellas Medivation, Janssen, Eisai, Bayer, Pfizer, Novartis, Exelixis, AstraZeneca. A Flechon: Honoraria: MSD Oncology, AstraZeneca, Bristol Myers Squibb, Janssen-Cilag, Astellas Pharma, Pfizer, Sanofi/Aventis, Roche/Genentech, Bayer, Ipsen, AAA HealthCare. Travel, Accommodations, Expenses: Astellas Pharma, Sanofi/Aventis, Janssen-Cilag, Bayer, Pfizer, Ipsen, Bristol Myers Squibb, AstraZeneca, MSD Oncology, Roche/Genentech, AAA HealthCare. R Jain: Honoraria: DAVA Oncology, Curio Science, FLASCO. Consulting or Advisory Role: BMS, EMD Serono, Gilead, Seattle Genetics, AVEO, Sanofi. Speakers' Bureau: Seattle Genetics. Research Funding: BMS, Gilead, CTEP. S Gupta: Stock and Other Ownership Interests: Salarius Pharmaceuticals (family member). Research Funding: Mirati Therapeutics, Novartis, Pfizer, Viralytics, Hoosier Cancer Research Network, Rexahn Pharmaceuticals, Five Prime Therapeutics, Incyte, MedImmune, Merck, Bristol

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