

## Clinical Results Summary

### A clinical study to learn about the safety and effects of DS-8201a in participants with advanced solid tumors

Thank You!



Daiichi Sankyo Co. Ltd., the sponsor of this study, would like to thank the participants who took part in this study for trastuzumab deruxtecan, also known DS-8201a or T-DXd. Each participant helped to advance medical research for people affected with advanced solid tumors. Their contribution to medicine and healthcare is greatly appreciated.

**Protocol number:** DS8201-A-J101

**Important note:** This summary only shows the results of a single study. Other studies may have different findings. Researchers and health authorities look at the results of many studies to understand which treatments work and how they work. It takes a lot of people in many studies around the world to advance medical science and healthcare.

Do not use the results of this study to make health decisions. Please talk to a doctor before changing any treatment you are taking or if you have any questions about these study results.

# What was the main purpose of this study?

## Advanced solid tumors

A tumor is an abnormal growth of cells in the body that starts in an organ, muscle, or bone of the body. An “advanced” solid tumor usually means one that has spread to other parts of the body. A certain kind of protein called a ‘kinase’ helps tumor cells divide and grow. It is believed that by stopping this protein from working, the growth of the tumor cells can be stopped.

Some people with solid tumors have an expression of a protein called HER2, which makes their cells grow and divide too fast. DS-8201a, also known as trastuzumab deruxtecan or (as used from this point) T-DXd, specifically binds to HER2-expressing cells to inhibit the cell growth and cause the death of target tumor cells.

Participants enrolled in this study had some of the following types of tumors:

- Breast cancer
- Stomach cancer
- Gastroesophageal junction (GEJ) cancer: cancer in the area where the esophagus (a tube that carries food from the mouth) joins the stomach
- Non-small cell lung cancer (NSCLC): a cancer in which tumor cells are formed in the tissues of the lungs
- Colorectal cancer: cancer of the colon or rectum at the end of digestive system
- Other solid tumors

At this time treatment options for the above mentioned cancers are:

- surgery
- radiation therapy - a treatment that uses radiation to kill cancer cells
- endocrine (hormone) therapy - a treatment that stops the growth of cancers that use hormones to grow. This is given for the treatment of breast cancer.
- chemotherapy – a treatment that uses drugs to kill cancer cells or stop them from growing and dividing

Current treatment options do not work in all patients, therefore new methods for treating these cancers are needed.

In this study, researchers wanted to learn about the safety and effects of T-DXd in participants with HER2- expressing solid tumors which are refractory. Refractory means that the cancer does not respond to or cannot be treated with available treatment options.

## Treatment given in this study

This study had 2 parts. Part 1 involved the administration of increasing doses of T-DXd to establish recommended and maximum doses for further study. Part 2 used the recommended doses established in Part 1 in patients with different forms of cancer.



### T-DXd

Drug being studied for the treatment of advanced solid tumors.

## Main goals of this study

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



**Part 1:** Which was the recommended and maximum dose of T-DXd?



**Parts 1 and 2:** How many participants had cancer that completely disappeared or became at least 30% smaller after treatment?

*This will be measured by imaging.*



**Parts 1 and 2:** How many participants had side effects during this study?

*The summary of side effects is presented in the section 'What medical problems did the study participants have'.*

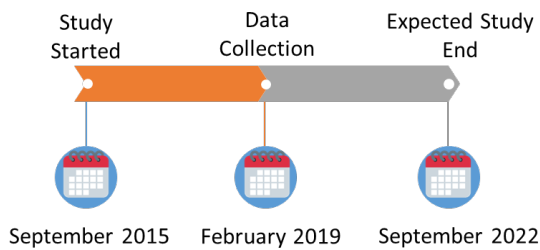
## Other goals of this study

Researchers also wanted to answer the following question:

- Parts 1 and 2: What were the exposure levels of T-DXd\*, its breakdown product MAAA-1181a, and total anti-HER2 antibody, in the blood of participants?

*\*T-DXd consists of 2 components connected by a linker. One component is a cytotoxic drug payload called DXd, or MAAA-1181a. The other is the HER2 targeted antibody called trastuzumab. The 2 components are designed to stay connected by the linker until T-DXd binds to a cancer cell with the HER2 marker on it. Once T-DXd binds to an HER2-expressing cancer cell, it gets activated. The 2 components then separate and the cytotoxic drug payload component (MAAA-1181a) kills the HER2-expressing cancer cell.*

## How long was this study?

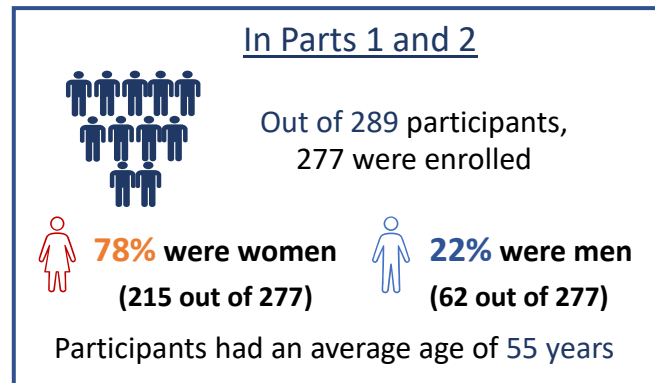
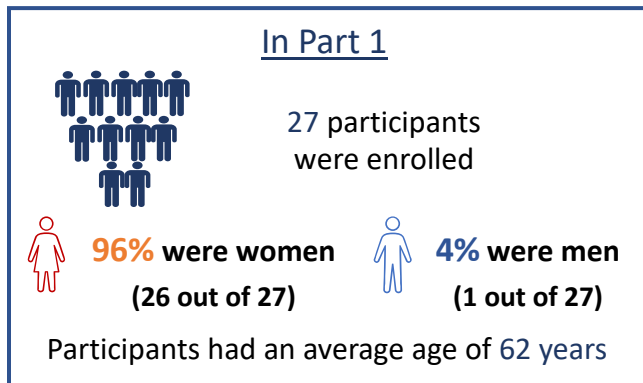


The study was designed so that participants could continue in it as long as their tumor did not get worse and they did not have serious side effects. The study started in September 2015 and is expected to end in September 2022.

The results were collected up to February 2019 and a study report was created. Once the study is completed, a full summary of the results will also be made available.

## Who was in this study?

This study included 289 participants from the United States and Japan. In Part 1 the dose was increased in steps from 0.8mg/kg to 8.0 mg/kg in order to establish the recommended dose for further study. Two doses, 5.4 mg/kg and 6.4 mg/kg, were selected for continued testing.



Participants could take part in this study if they:

- were at least 20 years old in Japan and at least 18 years old in the United States,
- were either fully active or unable to do a hard physical activity but able to walk and do light work,
- had one of the following advanced tumors that came back after standard treatment or could not be treated by standard treatment or for which no standard treatment was available:
  - **Part 1:** breast cancer, stomach cancer or GEJ cancer
  - **Part 2a:** breast cancer with an increased level of HER2 that had been previously treated with T-DM1 (also known as trastuzumab emtansine)
  - **Part 2b:** stomach or GEJ cancer with an increased level of HER2 that had been previously treated with trastuzumab
  - **Part 2c:** breast cancer with a low level of HER2
  - **Part 2d:** other solid cancers that spread to other parts of the body with HER2 expression
  - **Part 2e:** breast cancer with HER2 expression for which no standard treatment is available

## What happened during this study?

This was a Phase 1 study. Phase 1 studies are done to find out how new study treatment works in a small number of participants. This helps researchers understand what happens to the study treatment in the body, and if there are any side effects.

This was an “open label” study, which means that both the researchers and the participants knew what dose of T-DXd the participants were given.

Two types of drug products were used in this study. Participants in Part 1 and Parts 2a, 2b, 2c, and 2d received drug product formulation 1 (50mg/2.5 mL injection). Participants in Part 2e received drug product formulation 2 (100 mg/5 mL injection); Part 2e was conducted at Japanese sites only.

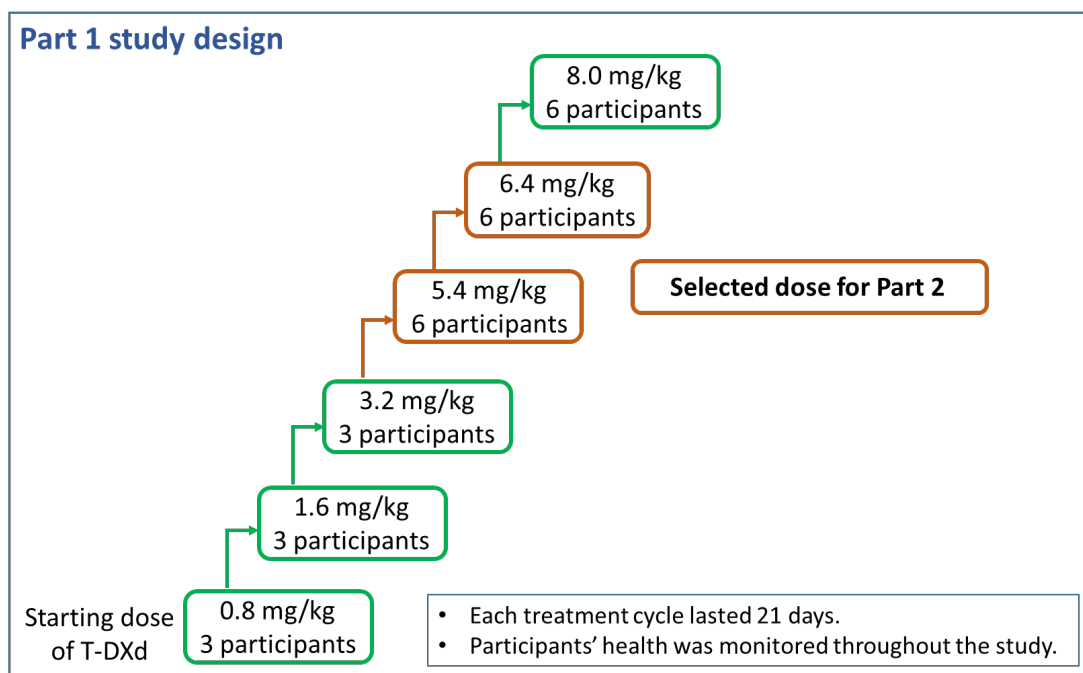
### Part 1

Part 1 of the study was called ‘dose escalation’. Dose escalation studies are done to find the maximum dose of a drug that can be safely given to participants and the dose that is recommended for further study.

In Part 1, 27 participants with advanced solid tumors were assigned to 6 groups. Researchers started by giving 0.8 milligrams (mg)/kg of T-DXd to the first group of participants. If this dose was considered to be safe by the researchers, the next group of participants received a higher dose of T-DXd. This process was repeated with increasingly higher doses, as shown in the study design figure below until the highest dose that could safely be given was identified.

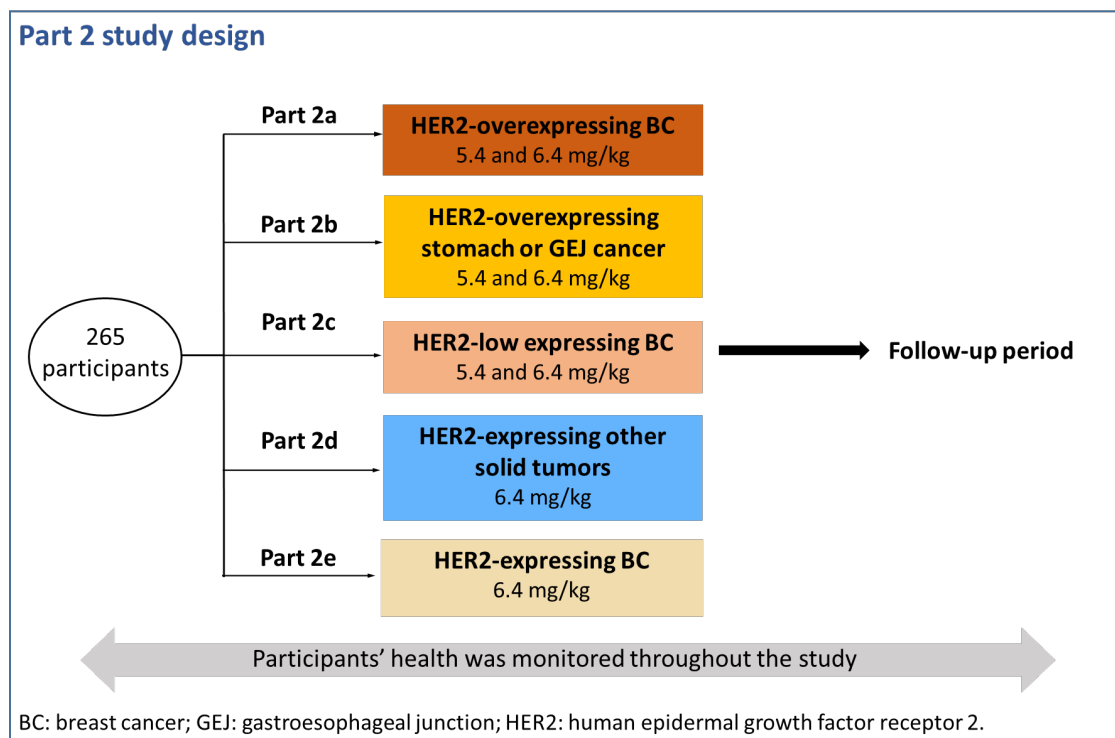
For all groups, T-DXd was given by injection every 3 weeks. Participants continued to receive treatment as long as they did not show worsening of their tumor or have serious side effects, or they asked to be removed from the study.

The maximum tolerated dose of T-DXd was not achieved in Part 1. The researchers identified 5.4 mg/kg and 6.4 mg/kg of T-DXd to be given to participants in Part 2.



## Part 2

Part 2 of the study was called 'dose expansion'. Dose expansion studies are done to find the safety and effects of the drug in a larger group of participants at the dose that was selected during dose escalation. In Part 2, 5.4 mg/kg or 6.4 mg/kg of T-DXd was given to participants with different types of solid tumors on the first day of successive 21-day cycles. For all groups, T-DXd was given directly into the vein.



## What were the key results of this study?

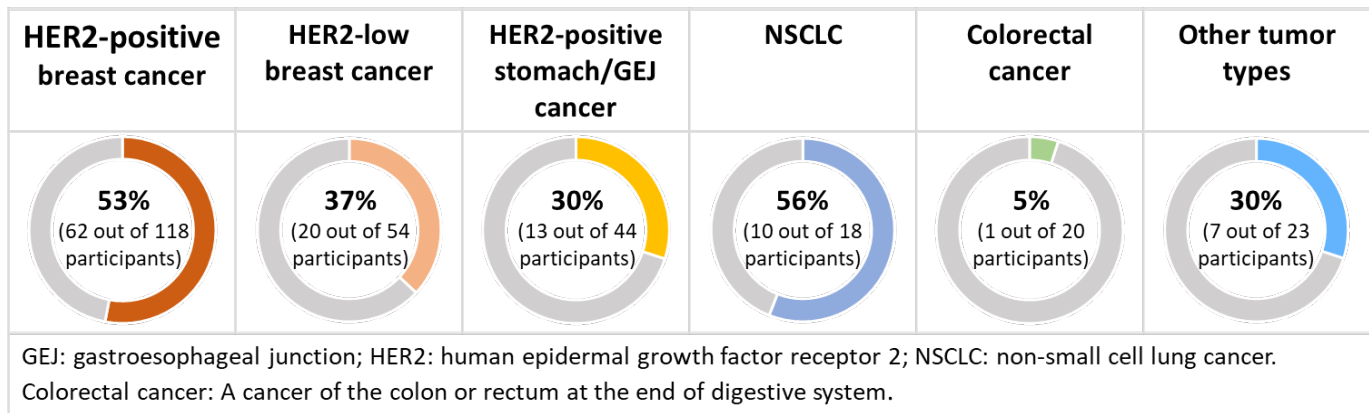
Key results from this study are shown for the total group of participants as average results. This summary does not show the results from each individual participant. An individual participant's results could be different from the total group of participants. A full list of the questions the researchers wanted to answer and a detailed presentation of the results can be found on the websites listed at the end of this summary.

### Part 1: Which was the recommended and maximum dose of T-DXd?

In this trial, doses of 5.4 mg/kg and 6.4 mg/kg were recommended for further study. The maximum dose of T-DXd patients could tolerate was not reached.

### Parts 1 and 2: How many participants had cancer that completely disappeared or became at least 30% smaller after treatment?

This was based on measures from imaging (scans). Results were available for 277 participants who were enrolled to either 5.4 mg/kg or 6.4 mg/kg of T-DXd. This included data from 12 participants from the dose escalation phase and 265 participants from dose expansion phase who received 5.4 mg/kg or 6.4 mg/kg of T-DXd.



## Parts 1 and 2: How many participants had side effects during this study?

Side effects are medical problems (such as a feeling tired) that happened during the study which the study doctor thought could be related to the treatments in the study.

The answers to this question are presented in the section ‘What medical problems did the study participants have’.

## What was the other result of this study?

### Parts 1 and 2: What were the exposure levels of T-DXd, its breakdown product MAAA-1181a, and total anti-HER2 antibody, in the blood of participants?

To answer this question, researchers measured the levels of T-DXd, MAAA-1181a, and anti-HER2 antibody in the participants’ blood for different doses after the first dose of treatment.

The average results of these measurements are presented below. Concentration of T-DXd, MAAA-1181a, and anti-HER2 antibody in the participants’ blood are measured in µg (micrograms) \* d/mL for T-DXd and ng (nanograms) \* d/mL for MAAA-1181a.

Researchers found that the total exposure levels of T-DXd, MAAA-1181a, and total anti-HER2 antibody in the participants’ blood increased with increasing doses.

#### Part 1 – Total exposure levels

Dose Escalation	0.8 mg/kg	1.6 mg/kg	3.2 mg/kg	5.4 mg/kg	6.4 mg/kg	8.0 mg/kg
<b>T-DXd</b>	52	116	325	544	901	996
<b>Anti-HER2 Antibody</b>	84	200	302	609	878	1120
<b>MAAA-1181a</b>	5	9	24	41	31	40



The total exposure levels of T-DXd, MAAA-1181a, and total anti-HER2 antibody in Parts 1 and 2 are presented by cancer type for the doses 5.4 mg/kg and 6.4 mg/kg as shown below. Researchers found that the total exposure levels of T-DXd in blood were higher at 6.4 mg/kg when compared to 5.4 mg/kg. The total exposure levels of total anti-HER2 antibody were similar to T-DXd. MAAA-1181a exposure levels were lower than that of T-DXd or total anti-HER2 antibody. However, the exposure levels of T-DXd and total anti-HER2 antibody in blood were lower in HER2-expressing GC high cancer.

### Parts 1 and 2 – Total exposure levels by 5.4 mg/kg dose

All participants	BC high 5.4 mg/kg	GC high 5.4 mg/kg	BC low 5.4 mg/kg
<b>T-DXd</b>	564	524	582
<b>Anti-HER2 Antibody</b>	771	683	659
<b>MAAA-1181a</b>	36	43	42

### Parts 1 and 2 – Total exposure levels by 6.4 mg/kg dose

All participants	BC high 6.4 mg/kg	GC high 6.4 mg/kg	BC low 6.4 mg/kg	Other 6.4 mg/kg
<b>T-DXd</b>	788	520	685	631
<b>Anti-HER2 Antibody</b>	1020	609	761	688
<b>MAAA-1181a</b>	42	43	44	49

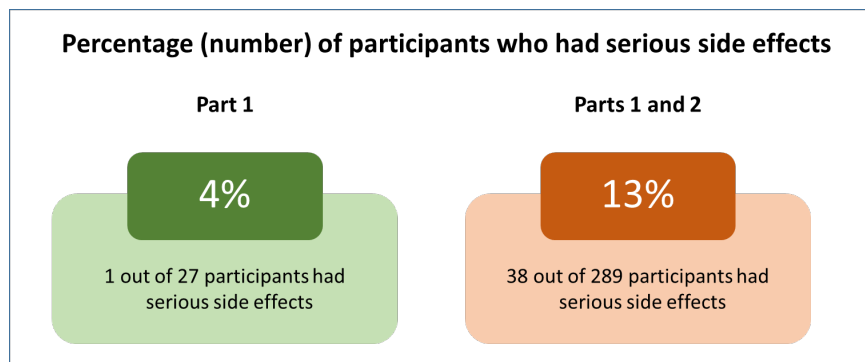
BC high: HER2-overexpressing breast cancer; GC high: HER2-overexpressing stomach or GEJ cancer; BC low: HER2-low expressing breast cancer.

## What medical problems did the study participants have?

Side effects are medical problems (such as a feeling tired) that happened during the study which the study doctor thought could be related to T-DXd. This section provides a summary of such side effects. These results were available for 289 participants who received any doses of T-DXd. The websites listed at the end of this summary has more information about the medical problems that happened in this study.

Side effects are considered serious if they cause death, are life-threatening, cause lasting problems, or require hospitalization. Some participants stop study treatment because of side effects.

## How many participants had serious side effects?



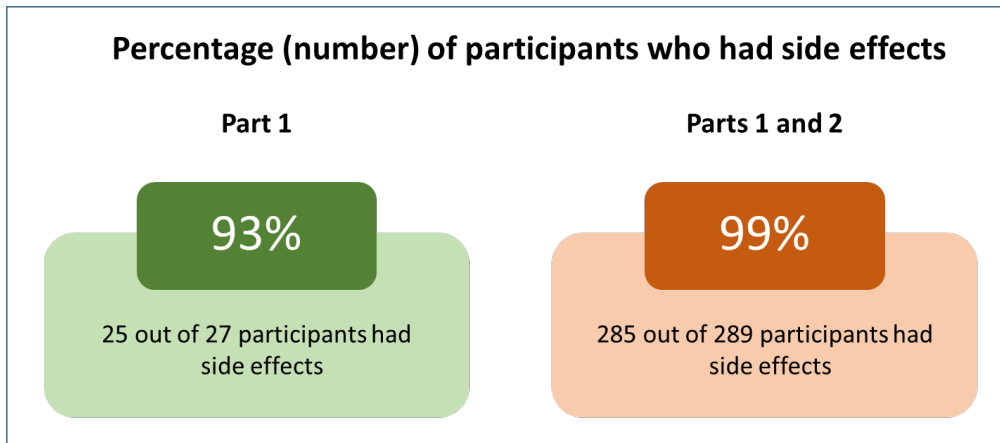
Overall, serious side effects observed by the dose group in **Parts 1 and 2** are presented below.

Treatment group by dose (Total number of participants)	5.4 mg/kg (91)	6.4 mg/kg (183)
Abnormally low number of neutrophils* accompanied with fever	1 (1%)	3 (2%)
Abnormally low number of platelets**	0	8 (4%)
Decrease in appetite	0	5 (3%)
Inflammation in the lung tissues	3 (3%)	7 (4%)
Insufficient oxygen in the lungs	1 (1%)	1 (1%)
Low number of red blood cells	1 (1%)	2 (1%)
Lung damage	0	3 (2%)

\*Neutrophils: Neutrophils are a type of white blood cell that help fight infection.  
 \*\*Platelets: Platelets are a type of blood cell that helps in preventing/stopping bleeding.

**6 participants (2%)** taking T-DXd died of causes associated with side effects during this study. The cause of death included lung damage or inflammation in the lung tissues, insufficient oxygen in the lungs, abnormally low number of neutrophils accompanied with fever, liver damage, and abnormal blood clotting in the blood vessels.

## How many participants had side effects?



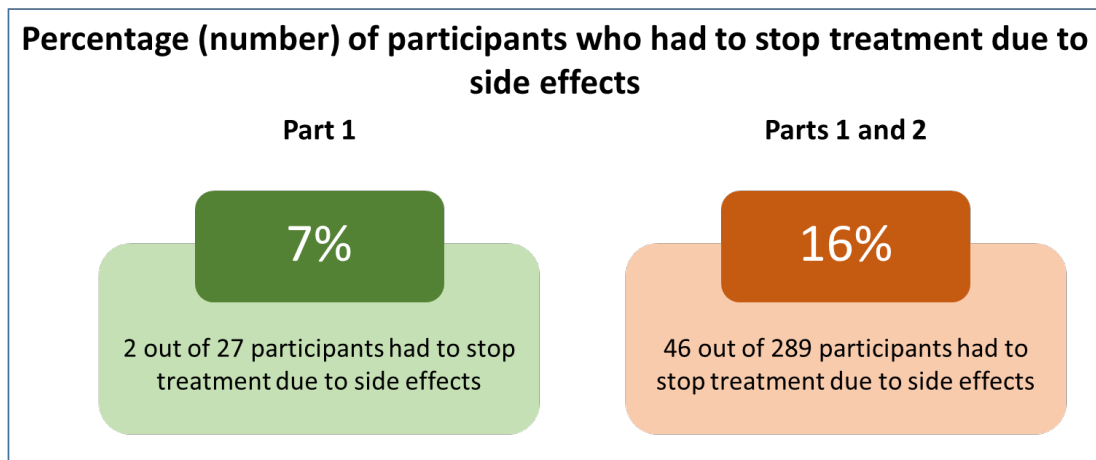
The most common side effects, which happened in at least 20% (20 out of 100) of participants in any dose group in **Parts 1 and 2** are presented below.

Treatment group by dose (Total number of participants)	5.4 mg/kg (91)	6.4 mg/kg (183)
Abnormally low number of platelets*	24 (26%)	71 (39%)
Abnormally low number of neutrophils**	16 (18%)	71 (39%)
Constipation	19 (21%)	47 (26%)
Decrease in appetite	34 (37%)	120 (66%)
Diarrhea	22 (24%)	55 (30%)
Feeling of discomfort	10 (11%)	48 (26%)
Feeling tired	37 (41%)	60 (33%)
Hair loss	28 (31%)	86 (47%)
Increase in liver test value of aspartate aminotransferase in the blood	12 (13%)	43 (24%)
Inflammation of the mouth and lips	11 (12%)	43 (24%)
Low number of red blood cells	31 (34%)	71 (39%)
Low number of white blood cells	16 (18%)	63 (34%)
Nausea	66 (73%)	138 (75%)
Vomiting	31 (34%)	83 (45%)

\*Platelets: Platelets are a type of blood cell that helps in preventing/stopping bleeding.

\*\*Neutrophils: Neutrophils are a type of white blood cell that help fight infection.

## How many participants had to stop treatment because of side effects?



## How was this study useful for patients and researchers?


This was a first in human study. It helped researchers learn about the safety and effects of T-DXd in participants with advanced solid tumors.


Findings from this study may be used in other studies to learn whether patients with advanced solid tumors are helped by this treatment. Other studies for T-DXd are ongoing.

This summary only shows the results of a single study. Other studies may have different findings. Please talk to a doctor before changing any treatment you are taking or if you have any questions about these study results.

### Where can I learn more about this study?

You can find more information about this study on the following websites:

 [www.clinicaltrials.gov](http://www.clinicaltrials.gov): Use the NCT identifier NCT02564900 in the search field.

 <https://www.clinicaltrials.jp>: Use the identifier JapicCTI-152978 in the search field.

Please remember that the results on these websites may be presented in a different way. 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 site.

**Full study title:** Phase 1, Two-part, Multicenter, Non-randomized, Open-label, Multiple-dose, First-in-human Study of DS-8201a, in Subjects with Advanced Solid Malignant Tumors

**Sponsor:** Daiichi Sankyo, Inc.

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**Date of this summary:** 28 June 2022

This summary was prepared by Syneos Health®.