Daiichi-Sankyo

Clinical Results Summary

A clinical study to learn about the effects of ritonavir and itraconazole on the levels of DS-8201a in the blood of participants with HER2 expressing advanced solid tumors

Protocol number:DS8201-A-A104

Thank You!

Daiichi Sankyo Co., LTD, the sponsor of this study, would like to thank the participants who took part in this study for DS-8201a, also known as Trastuzumab Deruxtecan (T-DXd). Each participant helped to advance medical research for people affected with HER2-expressing advanced solid tumors. Their contribution to medicine and healthcare is greatly appreciated.

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.

What is the role of HER2 in advanced solid tumor?

Some people with solid tumors produces a protein called HER2, which makes their cells grow and divide too fast. This is called HER2-expressing tumors.

Currently, treatments for advanced solid tumors are surgery, radiation therapy, hormone therapy, chemotherapy, and immunotherapy.

- Radiation therapy is a type of treatment that uses radiation to kill tumor cells.
- Hormone therapy is a treatment that stops the growth of tumor cells that use hormones to grow.
- Chemotherapy uses medicine to kill tumor cells or stop them from growing and dividing.
- Immunotherapy is a treatment that uses substances to modify the action of immune system. The immune system helps the body to fight tumor, infections, and other diseases.

However, these treatment options do not work in all patients. Therefore, new methods for treating these tumors are needed.

How does the study treatment work?

DS-8201a, also known as trastuzumab deruxtecan or T-DXd, specifically binds to HER2-expressing cells to stop or slow the cell growth and cause the death of target tumor cells.

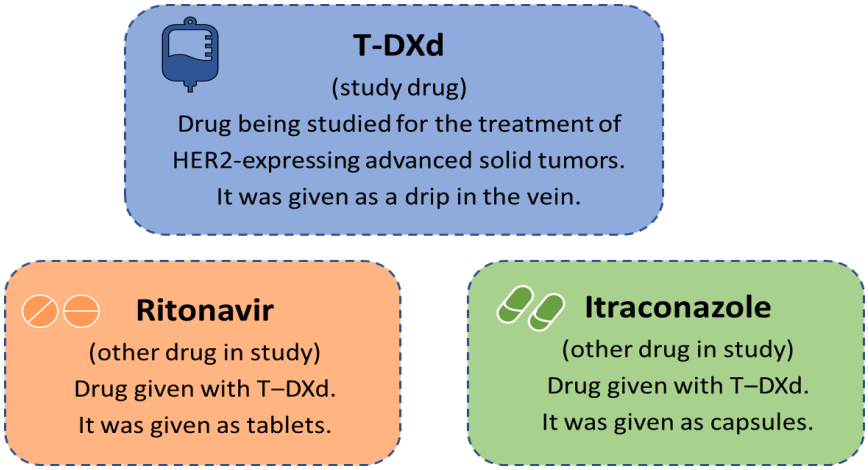
T-DXd consists of a drug called deruxtecanor DXd and a HER2 targeted antibody called trastuzumab. DXd and the antibody are designed to stay together until T-DXd binds to a cell with the HER2 expressing proteins on it. Once T-DXd binds to a HER2 expressing cell, it gets activated. DXd and the antibody then separate. DXd is the main active drug responsible to kill the HER2 expressing cell.

What other treatments are given in the study?

Ritonavir and itraconazole are drugs already available in the market. They are known to block proteins that are involved in break-down of drugs in the body and how it is removed from body. Ritonavir blocks two proteins called OATP1B and CYP3A, and itraconazole blocks the protein CYP3A. Taking either ritonavir or itraconazole with T-DXd may change the levels of DXd in the body.

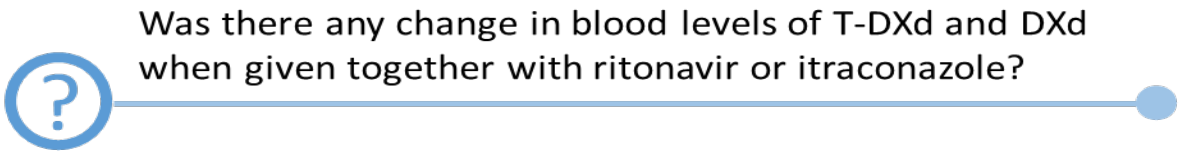
In this study, researchers wanted to learn about the effects of ritonavir and itraconazole on the levels of T-DXd and DXd in the blood of participants with HER2 expressing advanced solid tumors.

Treatments given in this study



Main purpose of this study

The main question the researchers wanted to answer in this study was:



*T-DXd consists a drug called deruxtecan (DXd) and a HER2 targeted antibody called trastuzumab.

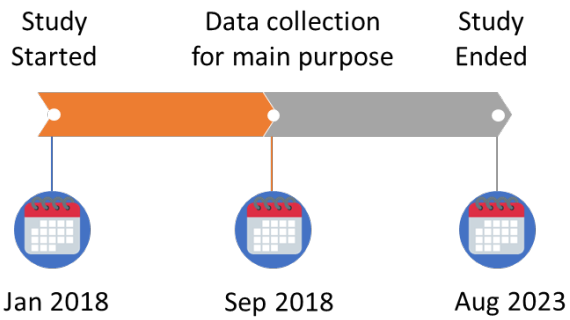
Other purposes of this study

Researchers also wanted to answer the following questions:

- How many participants had medical problems during the study?

Medical problems (such as a feeling tired) are adverse events that happened during the study and which the study doctor (investigator) thought that may or may not be related to any of the treatments in the study.

How long was this study?



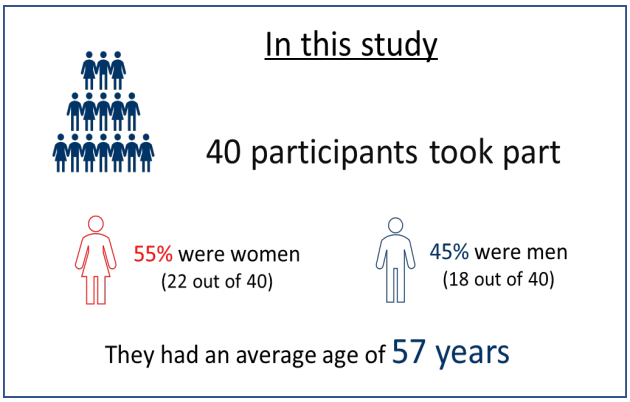
The study was designed so that participants could continue the treatment with T-DXd as long as their tumor did not get worse, they did not have side effects which led to discontinuation from study, or they left the study for any other reason. The study started in January 2018 and ended in August 2023.

Who was in this study?

This study included 40 participants from Japan, South Korea and Taiwan.

Participants could take part in this study if they:

- were 20 years or older.
- had HER2 expressing solid tumors which were advanced or could not be removed surgically, could not be treated with an earlier chemotherapy, or that did not have an available standard treatment.
- were either fully active or able to walk and do light work but unable to do a hard physical activity.
- had normal heart function before the start of the study and no heart attack within 6 months of the start of the study.
- could take ritonavir and itraconazole orally.



What happened during this study?

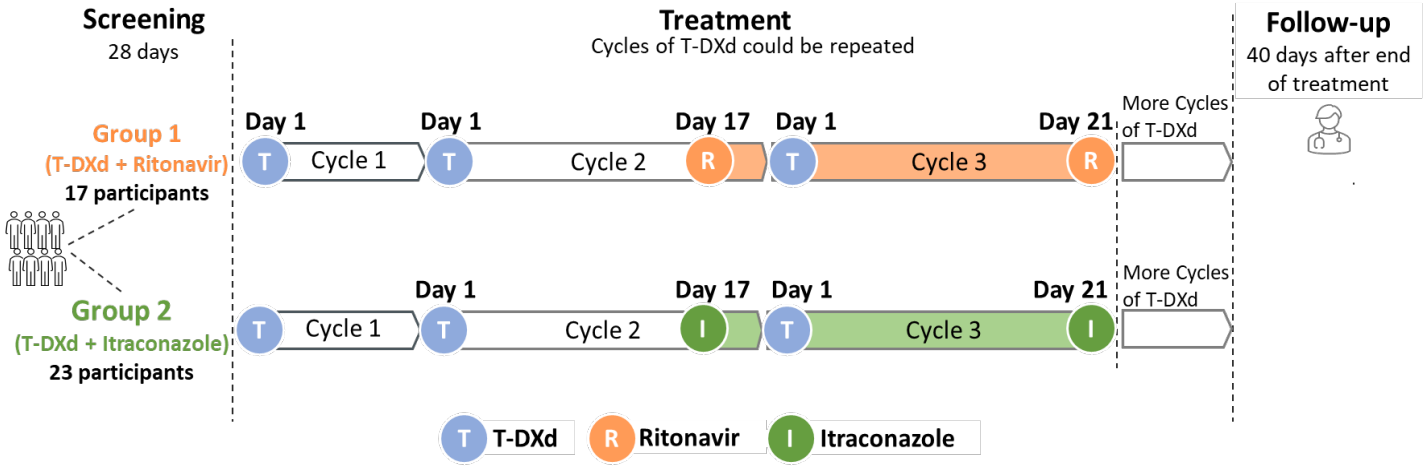
This was a Phase 1 study that looked at the effects of ritonavir and itraconazole on the blood levels of T-DXd and DXd. Phase 1 studies are done to find out how new study treatment works in a small number of patients. This helps researchers understand what happens to the study treatment in the body, and if there are any side effects. This study helped to understand what happened to T-DXd in the body when given along with ritonavir and itraconazole

This study was “open label”. This means that both the researchers and the participants knew which treatment was given to which participants.

The study included 40 participants. There were two groups in the study. In Group 1, the participants received T-DXd and ritonavir. In Group 2, the participants received T-DXd and itraconazole.

T-DXd was given at a dose of 5.4 milligram per kilogram (mg/kg) of body weight. All participants received T-DXd through a drip on the first day of each cycle. Each cycle lasted 3 weeks. Ritonavir and itraconazole were given from Day 17 of Cycle 2 until Day 21 of Cycle 3. In Group 1, ritonavir was given at a dose of 200 mg two times a day. In Group 2, itraconazole was given at a dose of 200 mg two times a day on Day 17 of Cycle 2 and then once a day from until the end of Cycle 3.

Participants continued to receive T-DXd for as long as their tumor did not get worse, they did not have side effects which led to discontinuation from study or they left the study for any other reason.



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 website listed at the end of this summary.

Was there any change in blood levels of T-DXd and DXd when given together with ritonavir or itraconazole?

To answer this question, the researchers measured the levels of T-DXd and DXd in the participants' blood samples on different days during Cycle 2 and Cycle 3. The levels of T-DXd and DXd measured during Cycle 2 was done before the participants received ritonavir or itraconazole. The levels of T-DXd and DXd measured during Cycle 3 was done after participants received ritonavir or itraconazole.

The researchers found a small change in the blood levels of T-DXd and DXd when given together with ritonavir or itraconazole. However, when they assessed this change along with the side effects, they concluded that overall it was not a meaningful change.

For Group 1 (T-DXd and ritonavir)

	Levels of T-DXd in blood		**Levels of DXd in blood**	
	Highest level (µg/ml)*	Total level (µg x d/ml)*	Highest level (ng/ml)*	Total level (ng x d/ml)*
Cycle 2 (before ritonavir)	133	650	9	33
Cycle 3 (after ritonavir)	140	754	9	37

For Group 2 (T-DXd and itraconazole)

	Levels of T-DXd in blood		Levels of DXd in blood	
	Highest level (µg/ml)*	Total level (µg x d/ml)*	Highest level (ng/ml)*	Total level (ng x d/ml)*
Cycle 2 (before itraconazole)	139	644	9	30
Cycle 3 (after itraconazole)	142	710	9	35

*The measured levels of T-DXd and DXd were in a tiny unit called micrograms (µg) or nanograms (ng) per milliliter (ml), which is one millionth of a gram or one thousand millionths of a gram in each milliliter of blood.
The highest level means the maximum blood levels observed during the observation period. Total level represents the amount of T-DXd and DXd in blood during observation period after treatment.

What were the other results of this study?

How many participants had medical problems during the study?

During this study, all the participants (17 out of 17) in Group 1 and 96% (22 out of 23) of the participants in Group 2 had at least 1 medical problem. These medical problems may or may not be related to any of the study treatments.

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 (investigator) thought could be related to any of the treatments in the study. This section provides a summary of side effects related to the study treatment. The website 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 disability, cause lasting problems, cause birth defects, or require hospitalization. Some participants stop study treatment because of side effects.

Side effects other than those related to study treatment are not reported here. For more information on medical problems, please visit the website listed at the end of this summary.

How many participants had serious side effects?

In this study, side effects were monitored for 17 participants in Group 1 who were given T-DXd with ritonavir and for 23 participants in Group 2 who were given T-DXd with itraconazole.

Serious side effects related to T-DXd:

12% (2 out of 17) of the participants in Group 1 and 4% (1 out of 23) of the participants in Group 2 had serious side effects.

Serious side effects related to Ritonavir or Itraconazole:

6% (1 out of 17) of the participants in Group 1 and none of the participants in Group 2 had serious side effects.

The serious side effects are presented below.

Side Effects	Related to T-DXd		Related to Ritonavir or Itraconazole	
	Group 1 (out of 17 participants)	Group 2 (out of 23 participants)	Group 1 (out of 17 participants)	Group 2 (out of 23 participants)
Inflammation in Lung	6% (1 participant)	0	6% (1 participant)	0
Diarrhea	0	4% (1 participant)	0	0
Feeling generally unwell	6% (1 participant)	0	0	0
Feeling sick	0	4% (1 participant)	0	0
Vomiting	0	4% (1 participant)	0	0

There were no deaths due to study treatment.

How many participants had side effects?

All side effects, both serious and non-serious, are presented in this section.

Side effects related to T-DXd:

All (17 out of 17) participants in Group 1 and 91% (21 out of 23) of the participants in Group 2 had the side effects.

Side effects related to Ritonavir or Itraconazole:

82% (14 out of 17) of the participants in Group 1 and 26% (6 out of 23) of the participants in Group 2 had the side effects.

The most common side effects, which happened in 30% or more participants in any group, are presented below.

Side Effects	Related to T-DXd (out of 40 participants)		Related to Ritonavir or Itraconazole (out of 40 participants)	
	Group 1 (out of 17 participants)	Group 2 (out of 23 participants)	Group 1 (out of 17 participants)	Group 2 (out of 23 participants)
Feeling sick	100% (17 participants)	70% (16 participants)	35% (6 participants)	9% (2 participants)
Decrease in appetite	77% (13 participants)	44% (10 participants)	0	0
Platelet count decreased	53% (9 participants)	17% (4 participants)	0	0
Decrease in white blood cell count	41% (7 participants)	30% (7 participants)	35% (6 participants)	0
Increase in liver test value of aspartate aminotransferase in the blood	41% (7 participants)	22% (5 participants)	0	0
Increase in liver test value of alanine aminotransferase in the blood	41% (7 participants)	13% (3 participants)	0	0
Bald patches on scalp	35% (6 participants)	35% (8 participants)	0	0
Decreased level of white blood cells called neutrophils	35% (6 participants)	44% (10 participants)	0	0
Decrease in red blood cells count	35% (6 participants)	17% (4 participants)	0	0
Diarrhea	35% (6 participants)	13% (3 participants)	41% (7 participants)	0
Feeling tired	24% (4 participants)	30% (7 participants)	0	0
Vomiting	18% (3 participants)	30% (7 participants)	0	0

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

Seven (7) out of 40 of participants who received T-DXd in either of the groups stopped treatment early because of side effects. The most common side effect that led to participants stopping study treatment was inflammation in lung.

Two (2) out of 40 of participants who received ritonavir or itraconazole stopped treatment early because of side effects. The side effects that led to participants stopping study treatment were decrease in white blood cell count, decreased in platelet count, and decrease in white blood cells called neutrophils.

How was this study useful for patients and researchers?

This study helped researchers learn about the effects of ritonavir and itraconazole on the levels of T-DXd in the blood of participants with HER2 expressing advanced solid tumors.

Findings from this study may be used in other studies to learn whether patients with HER2 expressing advanced solid tumors are helped by this treatment.

Other studies for T-DXd are ongoing.

Please remember, 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 website:

- www.clinicaltrials.gov: Use the NCT identifier NCT03383692 in the search field.

Please remember that the results on this website 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: A Phase 1, Multicenter, Open-Label, Single Sequence Crossover Study to Evaluate Drug-Drug Interaction Potential of OATP1B/CYP3A Inhibitor on the Pharmacokinetics of DS-8201a in Subjects with HER2-Expressing Advanced Solid Malignant Tumors

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