Clinical Results Summary

A first in human study of HER3-DXd in participants with advanced breast cancer

Protocol number: **U31402-A-J101**

Thank You!

Daiichi Sankyo, Inc., the sponsor of this study, would like to thank the participants who took part in this study of HER3-DXd, also known as patritumab deruxtecan or U3-1402. Each participant helped to advance medical research for people affected with advanced breast cancer. 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 breast cancer

Breast cancer occurs when abnormal cells in the breast grow in an uncontrolled way. It occurs in both men and women, but women are at greater risk due to breast development and lifelong exposure to certain hormones. These cancer cells divide more rapidly than normal healthy cells and form a lump or tumor. Symptoms of advanced breast cancer can include swelling in the breast, redness of the skin around the breast area, nipple discharge, weakness in any part of the body, headache, pain in the bones, difficulty in breathing, and chest pain.

Advanced cancer is a term to describe cancer that has spread to another part of the body or that cannot be surgically removed.

- Some breast cancers have increased levels of proteins called HER3 or HER2, which makes cancer cells grow and divide faster. This is called HER3 or HER2 positive breast cancer, respectively.
- If the cancer does not have increased levels of HER3 or HER2, it is called HER3 or HER2 negative breast cancer.

Some types of breast cancer are classified based on how they respond to hormones in the body as: hormone receptor (HR) positive, HR-negative, and triple-negative breast cancer (TNBC).

- HR-positive breast cancer grows in response to female hormones such as estrogen and progesterone.
- HR-negative breast cancer does not grow in response to these hormones.
- Triple-negative breast cancer does not have cell receptors for estrogen or progesterone, it is not HER2-positive, making it more difficult to treat compared to other types of breast cancer.

Currently, treatment options for breast cancer include surgery, radiation therapy, hormone therapy, chemotherapy and immunotherapy. Radiation therapy is a type of cancer treatment that uses radiation to kill cancer cells. Hormone therapy is a cancer treatment that works by stopping the growth of cancer cells that rely on hormones to grow. Chemotherapy uses medicine to kill cancer cells or stop them from growing and dividing. Immunotherapy uses substances to modify the action of the immune system. The immune system helps the body to fight infections, and diseases.

These treatment options are not effective for everyone, and even in people who initially benefit from treatment, control of the tumor can be lost over time. Therefore, new approaches for treating breast cancer are needed.

In this study, researchers wanted to learn about the safety and effects of HER3-DXd in people with advanced breast cancer.

Treatment given in this study

This study had 3 parts. In Parts 1 and 2, researchers gradually increased the doses of HER3-DXd to find the highest safe dose and the optimal dose for future use. In Part 3, the optimal dose from Part 2 was used to treat participants with different types of advanced breast cancer.

HER3-DXd

(Study drug)

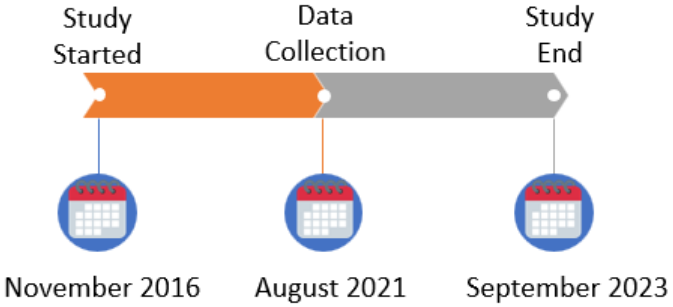
Different doses of HER3-DXd were given to treat participants with advanced breast cancer.

Main purpose of this study

The main questions the researchers wanted to answer in different parts of the study were:

- **Part 1: What was the highest safe dose of HER3-DXd?**
- **Part 2: What was the optimal dose of HER3-DXd?**
- **Part 2 and 3: How many participants had tumors that completely disappeared or became at least 30% smaller after treatment?**
- **Part 1, 2, and 3: How many participants had side effects during this study?**

How long was this study



The study was designed so that participants could continue in it as long as their cancer did not get worse, they did not have serious side effects which led to discontinuation from the study, or until they asked to be removed from the study. The study started in November 2016 and ended in September 2023.

Who was in this study?

This study included 182 female participants. Among these, 142 participants were from Japan and 40 participants were from the US.

Participants could take part in this study if they:

- were diagnosed with advanced breast cancer that could not be removed by surgery or had spread to another part of the body.
- were not responding to standard treatments or had side effects that prevented them from continuing those treatments, or standard treatments were no longer available for them.

In this study

182 female participants were enrolled

The average age of the participants was 56 years

- were either fully active or were unable to do a hard physical activity but were able to walk and do light work, and had not experienced any decline in their condition over the past 2 weeks.
- were expected to live for at least 3 more months.

Part 1 and Part 2

- were at least 20 years old if enrolled in Japan.
- had breast cancer with high levels of HER3.
- had prior treatment with at least 2 and up to 6 chemotherapy treatments for advanced breast cancer, and at least one treatment that included a drug called a taxane (specific to Part 2 and Part 3).

Part 3

- were at least 20 years old if enrolled in Japan and at least 18 years old if enrolled in the United States.
- had breast cancer with either high or low levels of HER3.
- were able to provide a new tumor sample before starting the study treatment, if they have not already provided one for HER3 testing.
- had breast cancer that was either HR-positive and HER2-negative, or HR-negative and HER2-negative *(participants with TNBC)*, and their condition met specific guidelines set by medical experts.
- had cancer which had worsened after receiving 1 to 2 previous chemotherapy treatments for advanced breast cancer *(participants with TNBC)*.

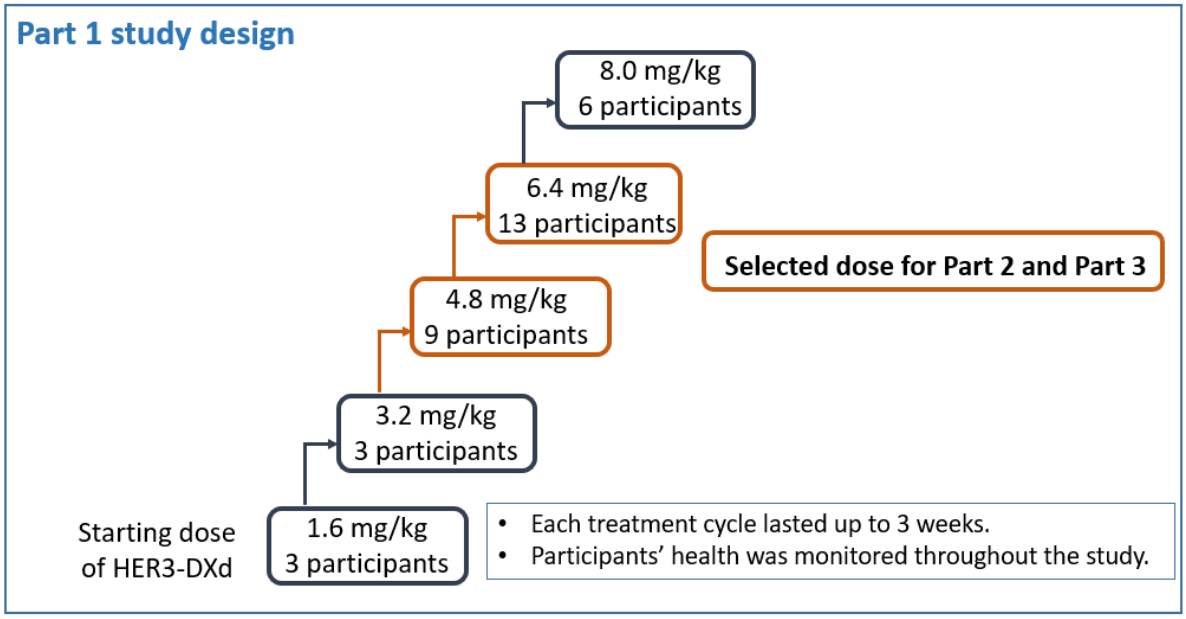
What happened during this study?

This was a Phase 1/ Phase 2 study, in which the study treatment is given to a small number of participants with advanced breast cancer to gather information about the safety and sometimes the effects of the study treatment, and then the number of participants is increased to gain a deeper understanding of safety and effects. This was a first-in-human study, which means that the study drug was tested for the first time in participants with cancer.

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

In this study, the researchers administered different doses of HER3-DXd once every cycle in 182 participants with advanced breast cancer. Each cycle lasted up to 3 weeks. All doses of HER3-DXd were given directly by infusing HER3-DXd through a needle into a vein. Participants continued to receive HER3-DXd as long as their cancer did not get worse, they did not have a serious side effect which led to discontinuation from the study, or until they ask to be removed from the study.

Part 1: Part 1 of the study was called 'dose escalation'. Dose escalation studies are done to find the highest safe dose of a drug that can be safely given to participants.



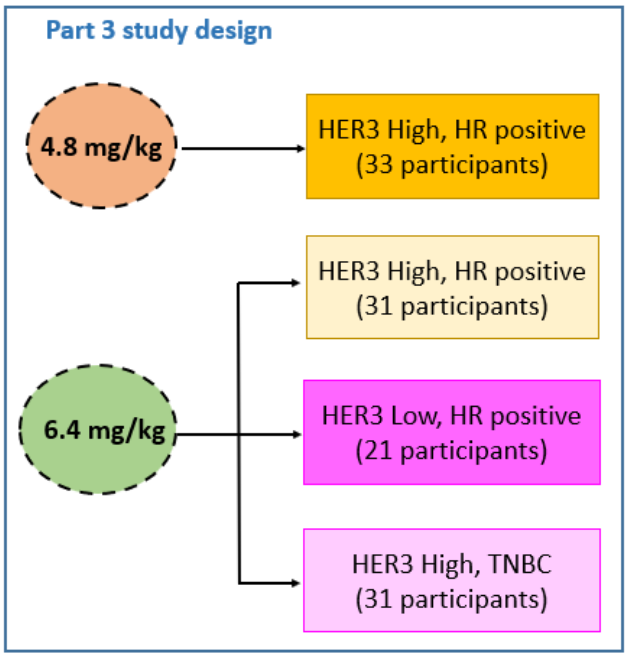
mg/kg=milligrams per kilogram of body weight.

Part 2: Part 2 of the study was called 'dose finding'. Dose finding studies are done to find the optimal dose for use in further parts of this study, and in future studies. Participants received different doses of HER3-DXd as shown in the table below. The researchers increased the dose gradually during the study.

HER3-DXd Dose	Number of participants
4.8 mg/kg	6
6.4 mg/kg	2
Cycle 1: 3.2 mg/kg Cycle 2: 4.8 mg/kg Cycle 3 and subsequent cycles: 6.4 mg/kg	12
Cycles 1, 2, and 3: 4.2 mg/kg (once every 2 weeks) Subsequent cycles: 6.4 mg/kg	12

mg/kg=milligrams per kilogram of body weight.

Part 3: Part 3 of the study was called 'dose expansion'. Dose expansion studies are done to deepen the understanding of the safety and effects of the drug in a larger group of participants at the dose that was selected during 'dose finding' part of the study. Participants with HER3-positive (HER3-High or HER3-Low), HER2 negative, HR-positive breast cancer and those with HER3-High TNBC advanced breast cancer were included in Part 3. Participants received HER3-DXd 4.8 mg/kg or 6.4 mg/kg.



The participants' health was monitored throughout the study.

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: What was the highest safe dose of HER3-DXd?

All doses of HER3-DXd tested in this study were tolerable, a highest safe dose was not reached.

Part 2: What was the recommended dose of HER3-DXd?

In this study, HER3-DXd doses of 4.8 mg/kg and 6.4 mg/kg were recommended for further use.

Part 2 and 3: How many participants had tumors that completely disappeared or became at least 30% smaller after treatment?

This was based on results from imaging (scans). Results were available for 170 participants. This included 54 participants from Part 1 and Part 2, and 116 participants from Part 3. The HER3-DXd doses that the participants received are shown as follows.

Part 1/Part 2	
4.8 mg/kg	**33%** (5 out of 15 participants)
6.4 mg/kg	**47%** (7 out of 15 participants)
Part 2	
3.2/4.8/6.4 mg/kg	**42%** (5 out of 12 participants)
4.2/6.4 mg/kg	**25%** (3 out of 12 participants)
Part 3	
4.8 mg/kg - HER3 High, HR Positive	**33%** (11 out of 33 participants)
6.4 mg/kg - HER3 High, HR Positive	**16%** (5 out of 31 participants)
6.4 mg/kg - HER3 Low, HR Positive	**33%** (7 out of 21 participants)
6.4 mg/kg - HER3 High, TNBC	**16%** (5 out of 31 participants)

Part 1, 2, and 3: 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 study treatment.

The answers to this question are presented in the section 'What side effects did the study participants have?'.

What side effects did the study participants have?

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 websites listed at the end of this summary.

How many participants had the most common serious side effects?

In this study, side effects were monitored for 182 participants given different doses of HER3-DXd.

Overall, 21% (38 out of 182) of participants who were given HER3-DXd reported serious side effects.

The most common serious side effects, which happened in at least 2 participants in any group are presented as % (number of participants) in the table below.

	Part 1/Part 2		Part 2		Part 3			
	4.8 mg/kg (15 participants)	6.4 mg/kg (15 participants)	3.2/4.8 /6.4 mg/kg (12 participants)	4.2/6.4 mg/kg (12 participants)	4.8 mg/kg - HER3 High, HR Positive (33 participants)	6.4 mg/kg - HER3 High, HR Positive (31 participants)	6.4 mg/kg - HER3 Low, HR Positive (21 participants)	6.4 mg/kg - HER3 High, TNBC (31 participants)
Platelet count decreased	7% (1)	13% (2)	8% (1)	0% (0)	0% (0)	10% (3)	0% (0)	3% (1)
Vomiting	0% (0)	0% (0)	17% (2)	17% (2)	6% (2)	0% (0)	5% (1)	0% (0)
Feeling sick (the desire to vomit)	0% (0)	0% (0)	8% (1)	17% (2)	3% (1)	0% (0)	5% (1)	7% (2)
Low number of white blood cells called neutrophils, and fever	0% (0)	0% (0)	0% (0)	0% (0)	3% (1)	0% (0)	10% (2)	3% (1)
Loss of appetite	7% (1)	7% (1)	0% (0)	0% (0)	6% (2)	3% (1)	5% (1)	3% (1)
Low blood platelet count	0% (0)	0% (0)	0% (0)	0% (0)	3% (1)	7% (2)	0% (0)	0% (0)

1 participant taking HER3-DXd died during this study. The cause of death was a severe infection with low white blood cell count.

How many participants had the most common side effects?

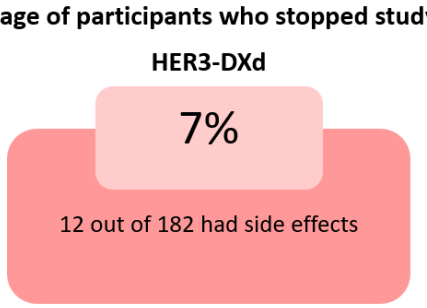
Overall, 99% (180 out of 182) of participants who were given HER3-DXd reported side effects. The most common side effects, which happened in at least 35% of participants in any group, are presented as % (number of participants) in the table below.

	Part 1/Part 2		Part 2		Part 3			
	4.8 mg/kg (15 participants)	6.4 mg/kg (15 participants)	3.2/4.8 /6.4 mg/kg (12 participants)	4.2/6.4 mg/kg (12 participants)	4.8 mg/kg - HER3 High, HR Positive (33 participants)	6.4 mg/kg - HER3 High, HR Positive (31 participants)	6.4 mg/kg - HER3 Low, HR Positive (21 participants)	6.4 mg/kg - HER3 High, TNBC (31 participants)
Feeling sick (the desire to vomit)	73% (11)	93% (14)	100% (12)	83% (10)	67% (22)	81% (25)	71% (15)	77% (24)
Increase of an enzyme called aspartate aminotransferase in the blood	67% (10)	40% (6)	25% (3)	8% (1)	27% (9)	23% (7)	24% (5)	32% (10)
Decreased number of white blood cells called neutrophils in the blood	67% (10)	87% (13)	67% (8)	25% (3)	46% (15)	32% (10)	38% (8)	48% (15)
Platelet count decreased	67% (10)	87% (13)	33% (4)	25% (3)	46% (15)	42% (13)	52% (11)	52% (16)
Increase of an enzyme called alanine aminotransferase in the blood	60% (9)	27% (4)	17% (2)	8% (1)	24% (8)	23% (7)	24% (5)	32% (10)

	Part 1/Part 2		Part 2		Part 3			
	4.8 mg/kg (15 participants)	6.4 mg/kg (15 participants)	3.2/4.8 /6.4 mg/kg (12 participants)	4.2/6.4 mg/kg (12 participants)	4.8 mg/kg - HER3 High, HR Positive (33 participants)	6.4 mg/kg - HER3 High, HR Positive (31 participants)	6.4 mg/kg - HER3 Low, HR Positive (21 participants)	6.4 mg/kg - HER3 High, TNBC (31 participants)
Loss of appetite	60% (9)	73% (11)	42% (5)	33% (4)	55% (18)	48% (15)	33% (7)	52% (16)
White blood cell count decreased	60% (9)	93% (14)	50% (6)	17% (2)	36% (12)	29% (9)	33% (7)	32% (10)
Decreased red blood cell count	47% (7)	47% (7)	33% (4)	8% (1)	33% (11)	58% (18)	24% (5)	32% (10)
Vomiting	47% (7)	47% (7)	33% (4)	25% (3)	46% (15)	36% (11)	29% (6)	48% (15)
Inflammation of the mouth and lips	40% (6)	40% (6)	17% (2)	17% (2)	18% (6)	16% (5)	48% (10)	39% (12)
Diarrhoea	33% (5)	53% (8)	42% (5)	50% (6)	30% (10)	39% (12)	24% (5)	36% (11)
Extreme tiredness	33% (5)	33% (5)	42% (5)	8% (1)	27% (9)	29% (9)	38% (8)	32% (10)
Uneasiness or lack of wellbeing	13% (2)	47% (7)	17% (2)	25% (3)	27% (9)	13% (4)	14% (3)	32% (10)

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

Overall, 7% (12 out of 182) of participants stopped treatment early because of side effects. The most common side effect that led to participants stopping study treatment early was inflammation of the lungs.



How was this study useful for patients and researchers?

This was a first in human study. This study helped researchers learn about the safety and effects of HER3-DXd in participants with advanced breast cancer.

Findings from this study may be used in other studies to learn whether participants with advanced breast cancer are helped by this treatment. Other studies for HER3-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 websites:

- www.clinicaltrials.gov: Use the NCT identifier NCT02980341 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 1/2, Multicenter, Open-Label, Multiple Dose, First-in-Human Study of U3-1402 in Subjects with HER3-Positive Metastatic Breast Cancer

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