Daiichi-Sankyo

Clinical Results Summary

A clinical study to learn about the safety and effects of pexidartinib when given with pembrolizumab in people with advanced skin cancer and other solid tumors

Protocol number: PLX108-14

Thank You!

Daiichi Sankyo, Inc., the sponsor of this study, would like to thank the participants who took part in this study for pexidartinib, also known PLX3397, when given with pembrolizumab. Each participant helped to advance medical research for people who have advanced skin cancer or other 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 melanoma and other solid tumors

Melanoma is a type of skin cancer in which tumors form when there is damage to melanin-producing cells. Melanin is a natural skin pigment that gives a dark color to skin, hair, and eyes. Melanomas can develop anywhere on the body. A solid tumor is a type of cancer or other abnormal growth that starts in an organ of the body.

Cancers are considered "advanced" if the cancer spreads to other parts of the body. Some people may have advanced melanoma or solid tumors that either do not respond to any of the treatments listed in the blue box on the right or come back after being treated. Therefore, new methods for treating advanced cancers are needed.

Current treatment options for advanced skin cancer and solid tumors:
Surgery: *operative or manual procedures to remove melanoma or tumor*
Chemotherapy: *uses medicines to kill cancer cells or to stop them from growing and dividing*
Radiation therapy: *uses X-rays to kill cancer cells*

Pexidartinib, also known as PLX3397, is being tested for its ability to reduce the growth of cancer cells. Pembrolizumab is an anti-cancer treatment which stimulates body's immune system to fight cancer cells. The immune system includes organs and processes of the body that provide resistance to infection and toxins. In this study, researchers wanted to understand the safety and effect of pexidartinib when given with pembrolizumab in participants with advanced melanoma and solid tumors.

This study had 2 parts. In Part 1, participants with any type of advanced solid tumor could enter. Part 2 was planned to include participants with advanced melanoma and selected advanced solid tumors (see page 7 and 8 for more details).

Treatments given in this study

Pexidartinib
(Study drug)

Drug being studied for the treatment of advanced melanoma and other solid tumors. When the study started, pexidartinib was not approved for use. This means that it could only be used in a research study such as this one.

Pembrolizumab
(Approved drug)

Approved treatment for melanoma and other types of cancers.

Main goal of this study

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

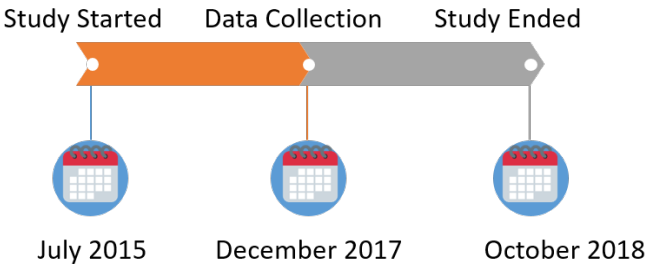
How many participants had side effects during this study?

Other goal of this study

Researchers also wanted to answer the following question:

- How many participants had tumors that completely disappeared or became at least 30% smaller after treatment with pexidartinib in addition to pembrolizumab?

How long was this study?



The study was designed in such a way that the participants could continue study treatment for up to 2 years as long as their cancer did not get worse and they did not have serious side effects.

The study started in July 2015 and was stopped early, in October 2018, because after Part 1 was completed, researchers could not find enough evidence that study treatment benefited the participants. By this time, 45 participants had already been enrolled in Part°2 of the study. The results were collected up to December 2017 for the study report. This summary is based on that report.

Who was in this study?

This study included 78 participants from 13 sites in the United States.

Participants could take part in this study if they:

- were 18 years of age or older
- had cancer that had re-occurred, spread to other parts of the body, did not respond to treatment, or for which no treatment was available
- were either fully active or unable to do a hard physical activity but able to walk and do light work

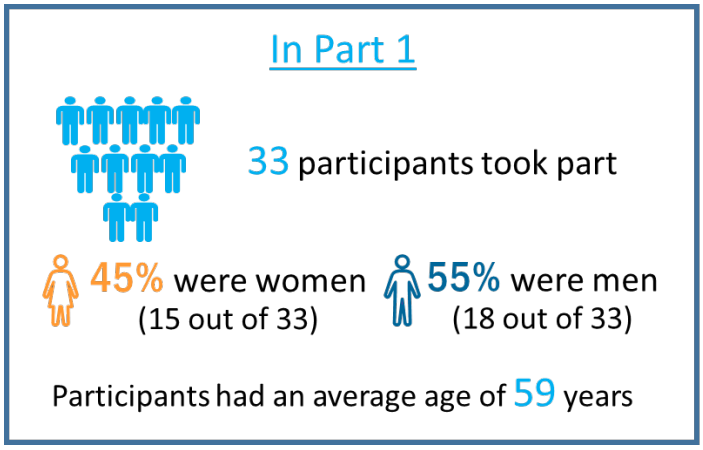
Part 1: had any type of advanced solid tumors

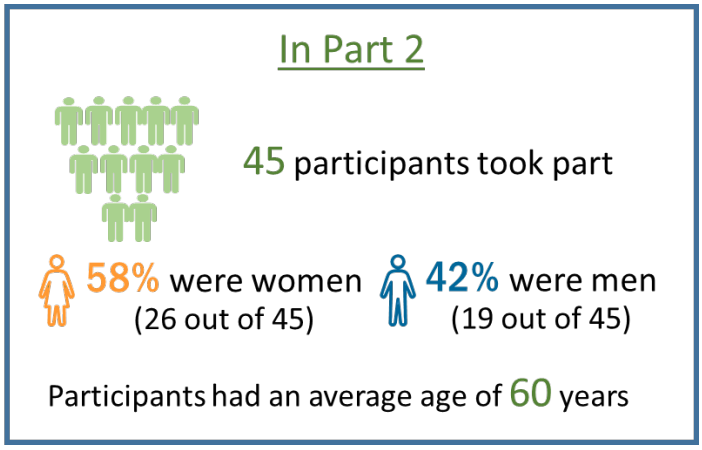
Part 2: had any one of the following tumor types:

- **non-small cell lung cancer**: a type of lung cancer
- **squamous cell cancer of the head and neck**: cancer that occurs in the outermost surface of the skin or certain tissues within the head and neck region including throat, mouth, sinuses and nose
- **melanoma**: skin cancer
- **ovarian cancer**: cancer of the ovaries (female organs that produce eggs)
- **renal cell carcinoma**: kidney cancer
- **grade 4 glioblastoma**: cancer of brain or spine which has spread to other parts of the body
- **gastro-intestinal stromal tumor**: stomach cancer

- **triple-negative breast cancer**: breast cancer
- **pancreatic ductal adenocarcinoma**: cancer of pancreatic duct (parts lying behind the lower part of the stomach)
- **gastric cancer**: stomach cancer
- **high grade soft tissue sarcoma**: cancer that begins in tissues, like muscles, tendon, fat, lymph and blood vessels, and nerves and is quickly spreading
- **cholangiocarcinoma**: cancer of the bile duct (tube that carries bile, the digestive fluid made by the liver between liver and gallbladder and the small intestine).

Part 2 was planned to include participants with any of the above tumor types. Following completion of Part 1, the sponsor decided to limit enrollment in Part 2 of the study to the following 5 types of cancer: melanoma, non-small cell lung cancer, ovarian cancer, squamous cell cancer of head and neck, and gastro-intestinal stromal tumor.





What happened during this study?

This was a Phase 1 and 2a study. Phase 1 studies are done to find the highest dose of a drug that can be safely given to participants who are receiving other therapy. Phase 2a studies are done to better understand if a drug can treat the condition it has been developed for.

This was an open-label study, which means that both the researchers and the participants knew which treatment was given to which participant.

Participants first completed a screening period to find out if they could take part in the study.

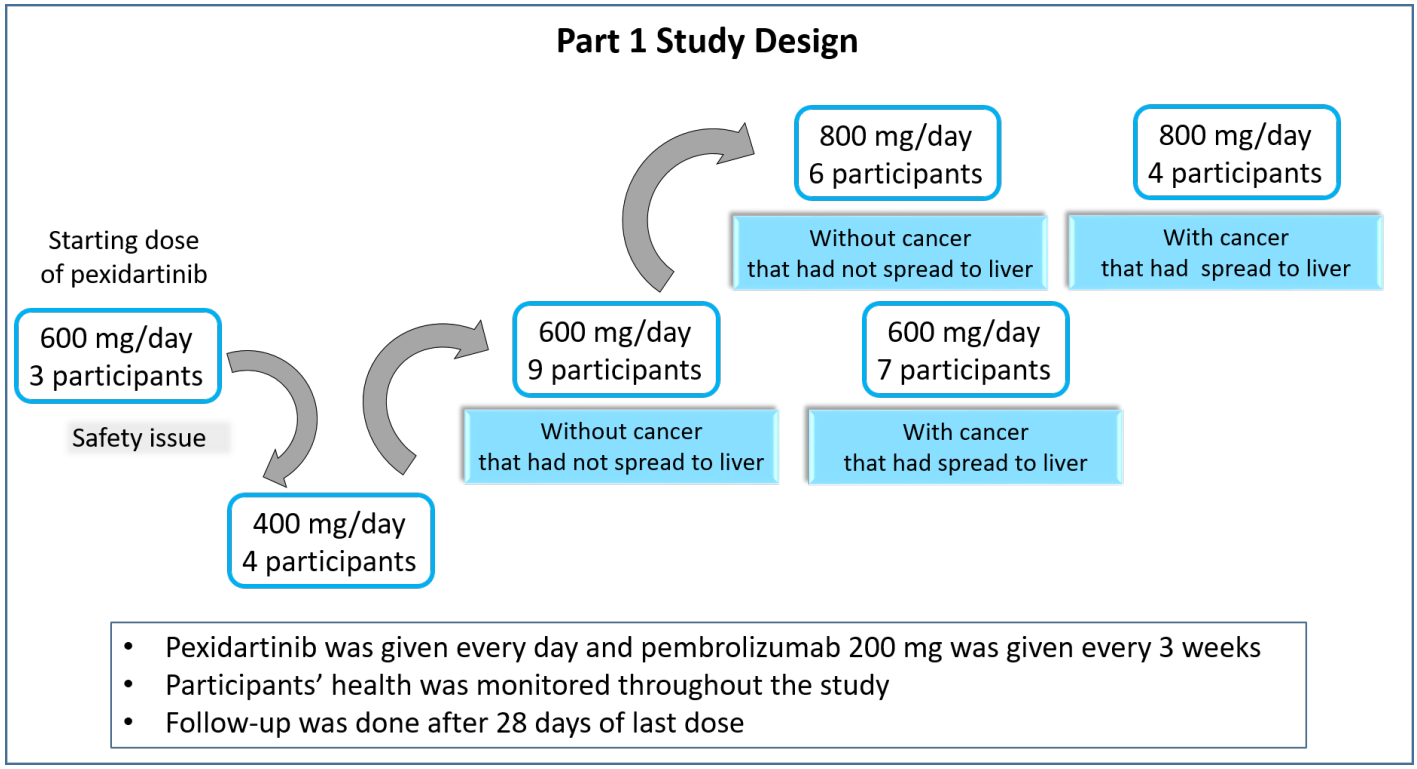
Part 1

Part 1 of this study was done to find the highest dose of pexidartinib that could safely be given to participants in addition to 200 milligrams (mg) pembrolizumab. All participants received pexidartinib capsules by mouth every day and pembrolizumab 200 mg infusion into the vein every 3 weeks.

The researchers started by giving 600 mg of pexidartinib, 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 pexidartinib. If this dose was considered not to be safe by the researchers, the next group of participants received a lower dose of pexidartinib. This process was repeated with increasingly higher doses until the highest dose that could safely be given was identified.

For all groups, pexidartinib was given by mouth as two divided doses, one in the morning and one in the evening each day.

The researchers identified 600 mg pexidartinib as the highest dose in Part 1 that could safely be given to participants. The different treatment groups are shown in the figure below.



Part 2

In Part 2, researchers gave the highest recommended dose of pexidartinib (600 mg) in addition to 200 mg pembrolizumab to participants with advanced melanoma and selected advanced solid tumors to find out if this combination was beneficial for them. In Part 2, 45 participants were divided into following 5 groups based on the cancer type they had:

- melanoma: 13 participants
- non-small cell lung cancer: 8 participants
- ovarian cancer: 15 participants
- squamous cell cancer of head and neck: 3 participants
- gastro-intestinal stromal tumor: 6 participants

All participants received pexidartinib 600 mg, capsules by mouth every day and pembrolizumab 200 mg infusion into the vein every 3 weeks.

The participants in this study continued to receive the treatment for up to 2 years as long as they did not show worsening of cancer, have serious side effects, or ask to be removed from the study.

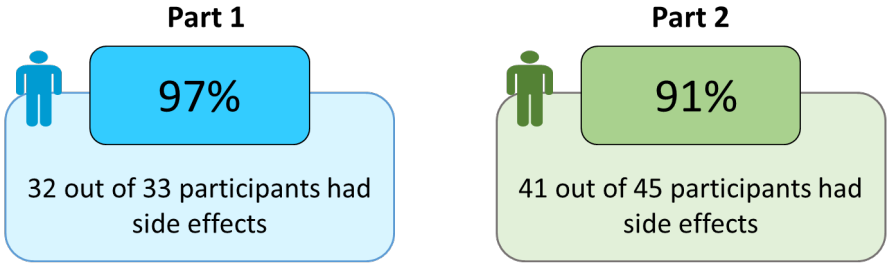
What were the key results of this study?

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 website listed at the end of this summary.

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.

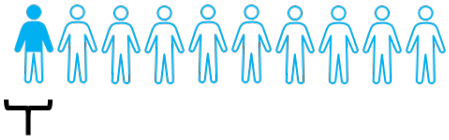
In this study, side effects were monitored for 78 participants in Part 1 and 2.



More detailed information about the side effects reported by participants is given below in the "Medical Problems" section of this summary.

What were the other results of this study?

How many participants had tumors that completely disappeared or became 30% smaller after treatment with pexidartinib in addition to pembrolizumab?

Part 1	Part 2
	
6% (2 out of 33) participants had at least 30% decrease in tumor size.	**7% (3 out of 45)** participants had at least 30% decrease in tumor size.
No participants had tumors that completely disappeared.	No participants had tumors that completely disappeared.

In Part 1, out of the 2 participants who had at least 30% reduction in tumor size:

- 1 participant received 600 mg per day of pexidartinib and had cancer that had spread to liver and
- 1 participant received 800 mg per day of pexidartinib and had cancer that had not spread to liver

In Part 2, 3 participants who had at least 30% reduction in tumor size and received 600 mg per day dose of pexidartinib:

- 2 participants had melanoma and
- 1 participant had ovarian cancer

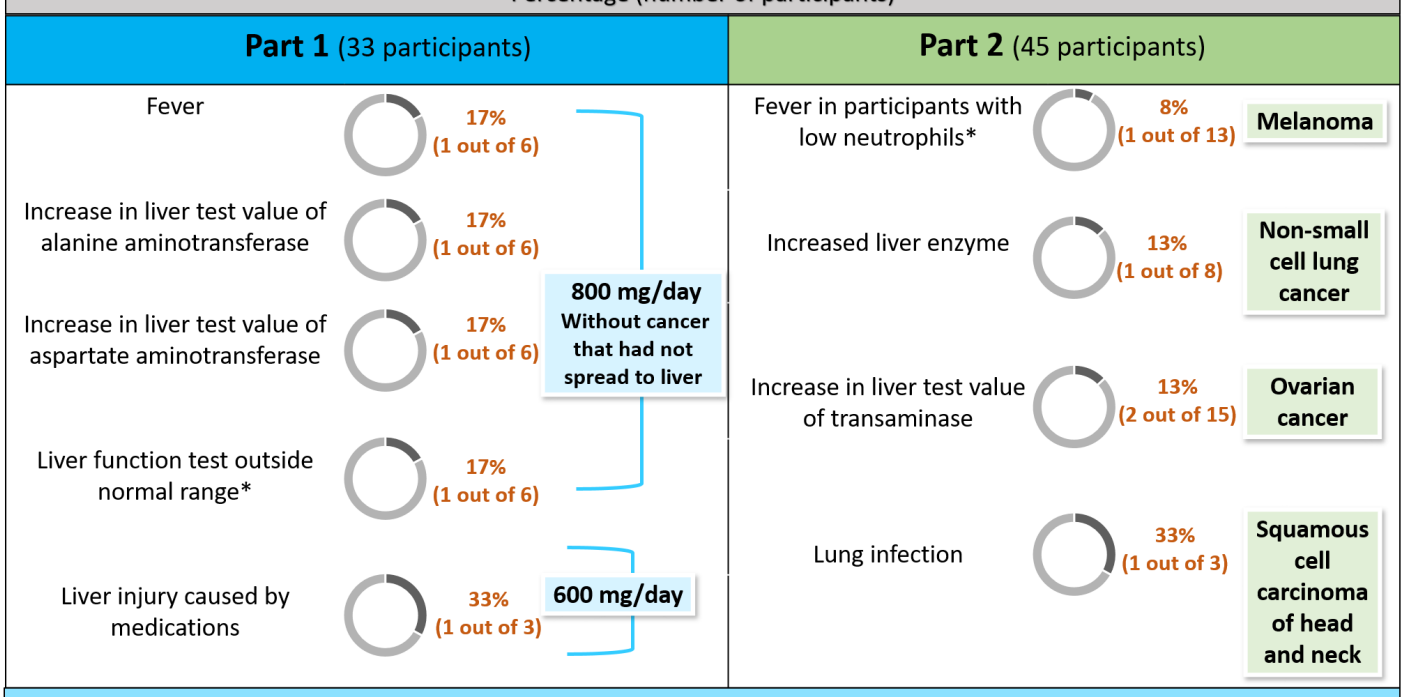
What medical problems did the study participants have?

This section provides a summary of side effects related to pexidartinib. 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 lasting problems, or require hospitalization. Some participants stop study treatment because of side effects.

How many participants had serious side effects?

Percentage of participants who had serious side effects related to pexidartinib
Percentage (number of participants)



* Liver function tests are blood tests that provide information about the state of the liver.
*Neutrophils are type of white blood cells that help fight infection.
Participants in Part 1 were given different doses of pexidartinib every day in addition to pembrolizumab 200 mg, every 3 weeks

Melanoma: *skin cancer*
Non-small cell lung cancer: a *type of lung cancer*
Ovarian cancer: *cancer of the ovaries*
Squamous cell carcinoma of head and neck: *cancer that occurs in the outermost surface of the skin or certain tissues within the head and neck region*
Participants in Part 2 were given pexidartinib 600 mg every day in addition to pembrolizumab 200 mg, every 3 weeks

There were no deaths reported in this study that were considered to be related to pexidartinib.

How many participants had most common side effects?

The most common side effects related to pexidartinib, both serious and non-serious, that occurred in at least 33% (33 out of 100) of participants in any group are reported below.

Most common side effects in Part 1 related to pexidartinib

Percentage (number of participants)

	400 mg/day	600 mg/day	600 mg/day With cancer that had spread to liver	600 mg/day Without cancer that had not spread to liver	800 mg/day With cancer that had spread to liver	800 mg/day Without cancer that had not spread to liver
Number of participants	**4**	**3**	**7**	**9**	**4**	**6**
Back pain	50% (2)	0	0	0	0	0
Diarrhea	0	0	0	33% (3)	0	0
Decreased appetite	25% (1)	0	14% (1)	11% (1)	0	33% (2)
Decrease in white blood cell counts*	0	0	0	22% (2)	0	33% (2)
Feeling sick to the stomach	0	0	29% (2)	33% (3)	75% (3)	17% (1)
Feeling tired	25% (1)	0	14% (1)	33% (3)	25% (1)	17% (1)
Hair color changes	0	0	0	0	0	33% (2)
Stomach pain	25% (1)	33% (1)	0	11% (1)	0	0
Increase of enzyme called alkaline phosphatase in blood	25% (1)	67% (2)	14% (1)	11% (1)	0	17% (1)
Increase in liver test value of alanine aminotransferase	0	67% (2)	14% (1)	0	25% (1)	50% (3)
Increase in liver test value of aspartate aminotransferase	25% (1)	67% (2)	29% (2)	33% (3)	25% (1)	50% (3)
Increase in blood bilirubin*	0	33% (1)	0	11% (1)	0	0
Increase in enzyme called gamma-glutamyltransferase	0	33% (1)	0	0	0	0
Liver injury caused by medications	0	33% (1)	0	0	0	0
Low blood platelet count	0	33% (1)	0	11% (1)	0	0
Raised red bumps on the skin	0	33% (1)	0	11% (1)	25% (1)	17% (1)
Swelling of the stomach	0	33% (1)	0	0	0	0

*White blood cells protect the body against infections.

*Bilirubin is a yellowish substance made during normal breakdown of red blood cells.

Participants were given different doses of pexidartinib every day in addition to pembrolizumab 200 mg, every 3 weeks

Most common side effects in Part 2 related to pexidartinib

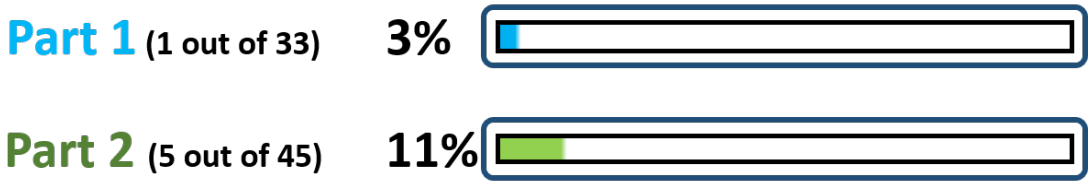
Percentage (number of participants)

	Melanoma	Non-small cell lung carcinoma	Ovarian cancer	Squamous cell carcinoma of head and neck	Gastro-intestinal stromal tumor
Number of participants	**13**	**8**	**15**	**3**	**6**
Change in taste	23% (3)	13% (1)	7% (1)	33% (1)	0
Decreased appetite	23% (3)	13% (1)	27% (4)	33% (1)	0
Decreased production of thyroid hormone	0	0	0	33% (1)	0
Decrease in white blood cell count*	23% (3)	0	7% (1)	0	33% (2)
Dry mouth	8% (1)	13% (1)	7% (1)	33% (1)	17% (1)
Feeling tired	46% (6)	25% (2)	47% (7)	0	50% (3)
Feeling sick to the stomach	23% (3)	38% (3)	27% (4)	100% (3)	17% (1)
Increase in liver test value of alanine aminotransferase	38% (5)	38% (3)	60% (9)	33% (1)	67% (4)
Increase in liver test value of aspartate aminotransferase	38% (5)	38% (3)	53% (8)	33% (1)	67% (4)
Itch	23% (3)	50% (4)	0	0	0
Itchy skin	0	0	7% (1)	33% (1)	0
Low white blood cells*	0	0	7% (1)	33% (1)	0
Lung infection	0	0	0	33% (1)	0
Raised red bumps on the skin	31% (4)	25% (2)	40% (6)	0	50% (3)

*White blood cells protect the body against infections.

Melanoma: *skin cancer*
Non-small cell lung cancer: *type of lung cancer*
Ovarian cancer: *cancer of the ovaries*
Squamous cell carcinoma of head and neck: *cancer that occurs in the outermost surface of the skin or certain tissues within the head and neck region*
Participants were given pexidartinib 600 mg every day in addition to pembrolizumab 200 mg, every 3 weeks

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



In part 1, the participant stopped taking pexidartinib due to side effects of liver function test outside normal range.

In part 2, the side effects that led to participants' stopping pexidartinib were increase in liver test values of alanine aminotransferase, aspartate aminotransferase, and transaminases, and feeling tired.

How was this study useful for patients and researchers?

This study helped researchers learn about the safety and effects of pexidartinib when given in addition to pembrolizumab in patients with skin cancer and other solid tumors. The study was stopped early because researchers could not find enough evidence that the study treatment benefited the participants.

Findings from this study may be used in other studies to learn whether patients with advanced melanoma and other solid tumors are helped by this treatment. Other studies for pexidartinib 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 NCT02452424 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:

Phase 1/2a Study of Double-immune Suppression Blockade by Combining a CSF1R Inhibitor (PLX3397) with an Anti-PD-1 Antibody (Pembrolizumab) to Treat Advanced Melanoma and Other Solid Tumors

Sponsor: Daiichi Sankyo, Inc.

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