Clinical Results Summary

A clinical study to learn about the effect of PLX3397 when given to people with solid tumors

Protocol number: PLX108-01

Thank You!

Daiichi Sankyo, Inc., the sponsor of this study, would like to thank the participants who took part in this study for PLX3397, also known as pexidartinib. Each participant helped to advance medical research for people with 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?

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. PLX3397, also known as pexidartinib, is a study drug that is being tested for its ability to stop the growth of tumor cells by preventing this protein from working.

In this study, researchers wanted to test the ability of PLX3397 to reduce the growth of tumor cells. Researchers also wanted to learn about the safety and other effects of PLX3397 in the body when given at the highest safe dose.

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

- mucoepidermal carcinoma (MEC) of the salivary gland: tumors in the glands that produce saliva
- gastrointestinal stromal tumor (GIST): tumors in the stomach or small intestine
- anaplastic thyroid carcinoma (ATC): aggressive form of tumor in the thyroid glands
- malignant effusion: fluid accumulation from a tumor between the chest wall and lungs
- pigmented villonodular synovitis (PVNS): tumors in the thin layer of tissue that lines the joints; PVNS is also known as diffuse type tenosynovial giant cell tumor
- other types of tumors that researchers believed could benefit from treatment with PLX3397

In this summary, results are presented as a comparison between 2 groups: participants with PVNS and all other participants. All other participants include participants with MEC, GIST, ATC, malignant effusion, and other types of tumors.

Treatment given in this study

PLX3397

Drug being studied for the treatment of solid tumors caused by certain kinases. When the study started, PLX3397 was not approved for use. This means that it could only be used in a research study such as this one.

Main goals of this study

The main questions the researchers wanted to answer in **Part 1** were:

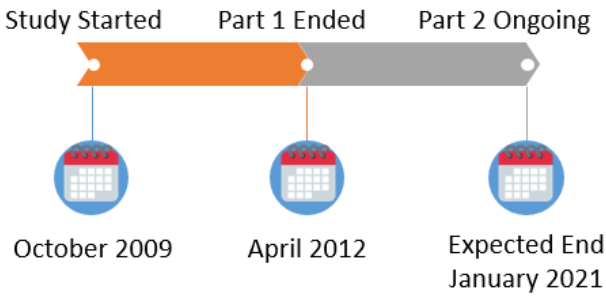
- What were the levels of PLX3397 in the blood of participants?
- How many participants had tumors that completely disappeared or became at least 30% smaller after treatment?
- What medical problems did the participants have during the study?

The main questions the researchers wanted to answer in **Part 2** were:

- How many participants had tumors that completely disappeared or became at least 30% smaller after treatment?
- For participants who had tumors that completely disappeared or decreased at least 30% in size, how long did that response to treatment last?
- How did participants in the PVNS group rate their change in symptoms after 2 months of treatment?

The health of participants was also monitored throughout the study.

How long was this study?

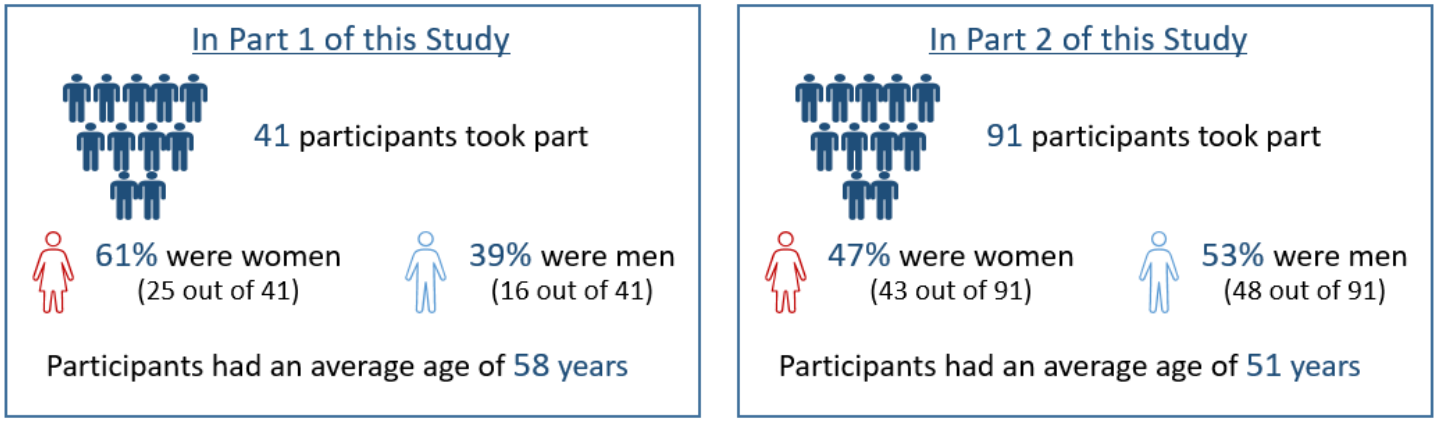


The study was designed so that participants could continue in it as long as their tumor did not get worse and they did not have serious side effects.

Results were collected up to 31 January 2018 and a study report was created. This summary is based on that report.

Who was in this study?

This study included 132 participants from the United States.



Participants could take part in this study if they:

- had advanced solid tumors that were measurable and believed to be caused by certain kinases,
- were expected to live for at least 3 months,
- had tumors that came back after standard treatment or could not be treated by standard treatment,
- were either fully active, OR unable to do hard physical activity but able to walk and do light housework or office work, OR unable to work but able to walk and manage self-care and be out of bed for more than 50% of waking hours,
- had adequate blood, liver, and kidney function, and
- met the criteria required to be included for each of the types of advanced solid tumors in Part 2.

What happened during this study?

This was a Phase 1 study. Phase 1 studies are done to find out how a new study drug works in a small number of participants.

Part 1

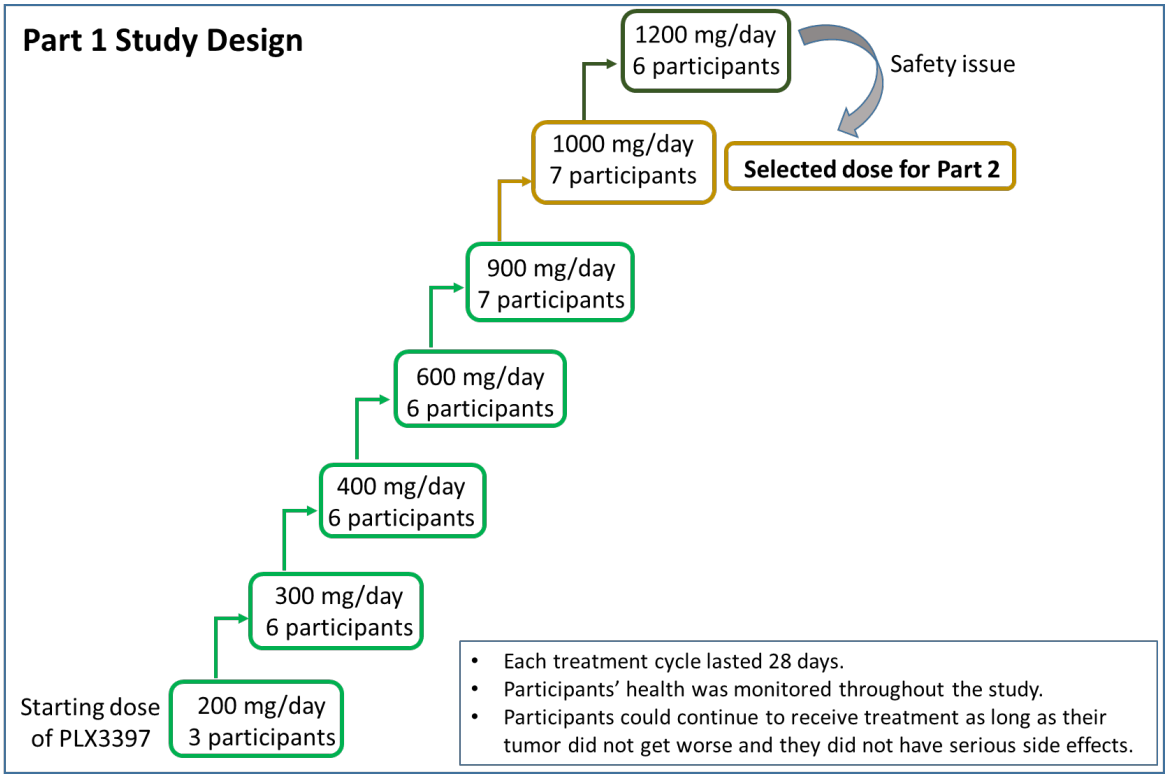
Part 1 of the study was called ‘dose escalation’. Dose escalation studies are done to find the highest dose of a drug that can be safely given to participants.

In Part 1, 41 participants with advanced solid tumors were assigned to 7 groups. Researchers started by giving 200 milligrams (mg) of PLX3397 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 PLX3397. 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 doses of 900 mg/day or less, PLX3397 was given by mouth once daily. For doses of 1000 mg/day and 1200 mg/day, PLX3397 was given by mouth as 2 divided doses, one in the morning and one in the evening each day. For example, the 1000 mg/day group received 500 mg in the morning and 500 mg in the evening.

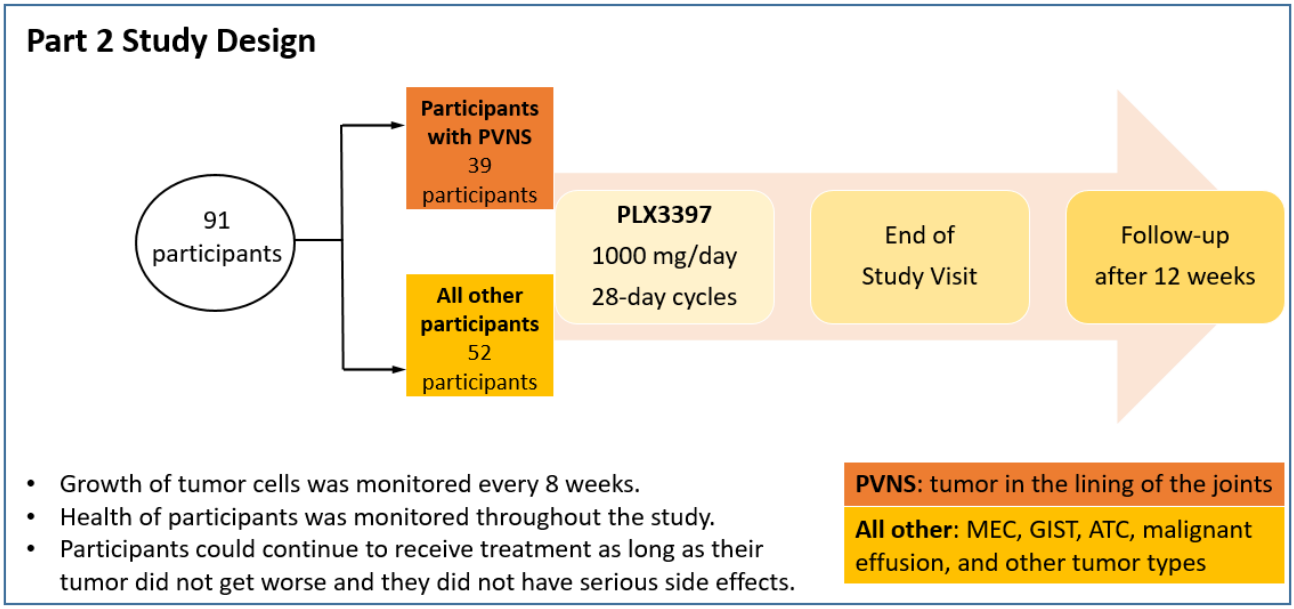
Participants continued to receive treatment as long as they did not show worsening of their tumor, have serious side effects, or asked to be removed from the study.

The researchers identified 1000 mg as the highest dose of PLX3397 that could safely be given to participants.



Part 2

Part 2 of the study was called 'dose extension'. In this part, the highest dose of PLX3397 that was identified in Part 1 (1000 mg) was given to participants with different types of solid tumors for 28-day cycles.



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.

Part 1

What were the levels of PLX3397 in the blood of participants?

To answer this question, researchers measured the following:

- Total level of PLX3397 in the participants' blood on Day 15 of treatment.
- Highest level of PLX3397 in the participants' blood on Day 15 of treatment.

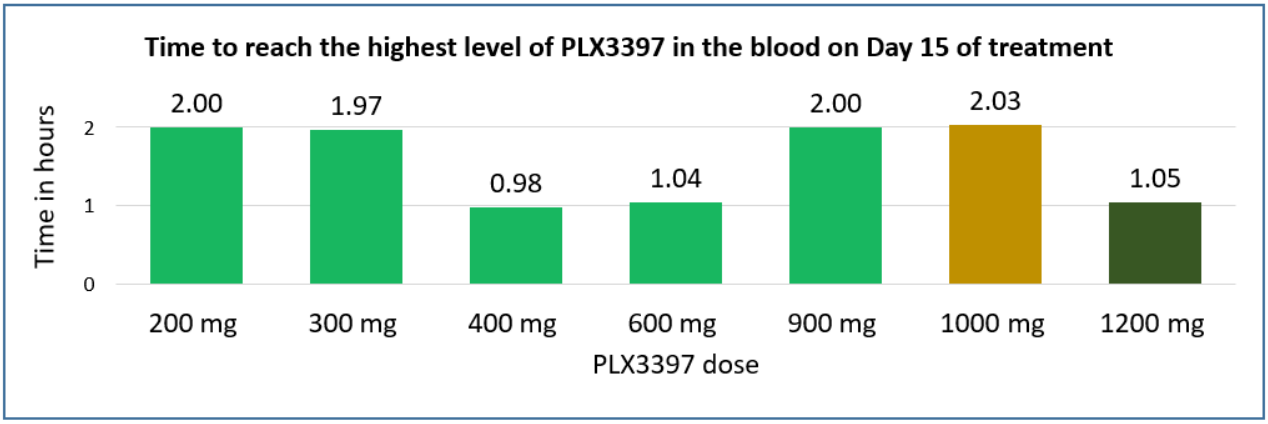
Researchers also measured how much time it took to reach the highest level of PLX3397 in the blood.

The median results of these measurements are presented below. This means that the levels for about half the participants were lower than these values and for the other half, the values were higher. Total level of PLX3397 in the participants' blood is measured in ng*hr/mL. This means the amount of PLX3397 in nanograms (one thousand-millionth of a gram) that was found in each milliliter of blood over time.

Levels of PLX3397 in the blood on Day 15 of treatment

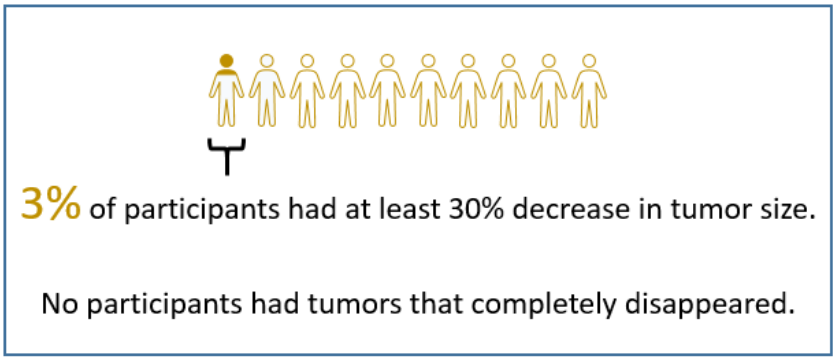
	200 mg	300 mg	400 mg	600 mg	900 mg	1000 mg	1200 mg
Total level (ng*hr/mL)	26200	50400	40500	81000	107000	115000	173000
Highest level (ng/mL)	1730	3630	3160	6570	6290	6320	10600

The time it took to reach the highest level of PLX3397 in the blood for each dose is presented below.



How many participants had tumors that completely disappeared or became at least 30% smaller after treatment?

These results were available for 35 participants. 3% (1 of 35) of participants had tumors that became at least 30% smaller after about 2 months of treatment in Part 1. This participant had tumors in the glands that produce saliva and received the 1000 mg/day dose of PLX3397.



What medical problems did the study participants have?

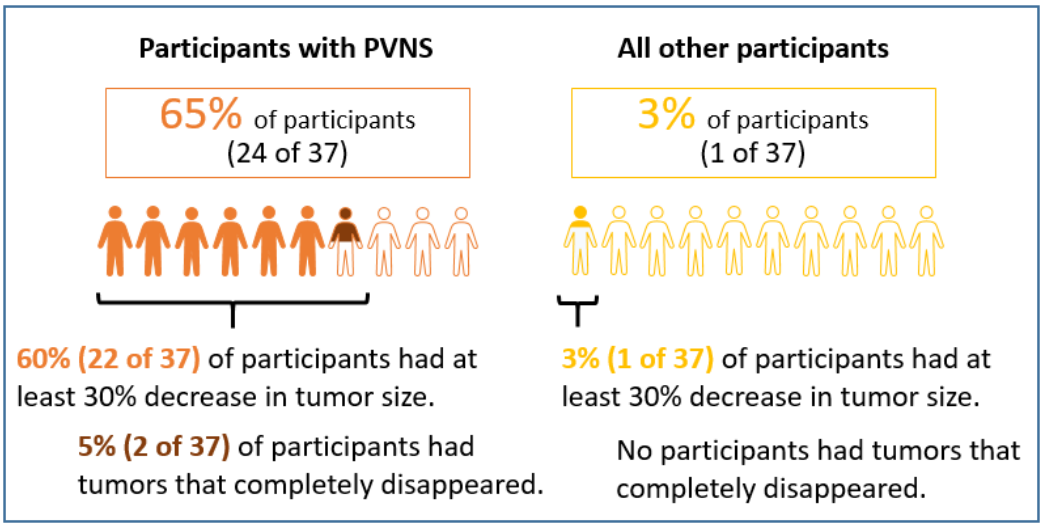
In Part 1 of this study, side effects were monitored for 41 participants. Out of 41 participants, 30 participants (73%) reported side effects related to PLX3397.

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

Part 2

How many participants had tumors that completely disappeared or became at least 30% smaller after treatment?

The participants who had tumors that completely disappeared or became at least 30% smaller after treatment in Part 2 are presented below. These results were available for 37 participants in each group. The group of participants with PVNS received treatment ranging from 15 days to about 4 years. The group of all other participants received treatment ranging from 1 day to about 1 year and 4 months.



For participants who had tumors that completely disappeared or decreased at least 30% in size, how long did that response to treatment last?

In Part 2 of the study, about half of the participants with PVNS maintained the response to treatment for about 31 months. In the group with all other participants, the participant who had at least a 30% decrease in tumor size maintained that response for about 4 months.

How did participants in the PVNS group rate their change in symptoms after 2 months of treatment?

In Part 2 of the study, 22 participants in the PVNS group filled out a survey both before and during treatment to rate the severity of their symptoms on a scale of 0 to 10. This survey included symptoms such as pain, swelling, stiffness, instability, and limited motion. For pain, 0 indicated "no pain" and 10 indicated "pain as bad as you can imagine". For the other symptoms, 0 indicated "no (symptom)" and 10 indicated "(symptom) worst imaginable".

There was an improvement in all symptoms after 2 months of treatment, as compared with the start of the study. However, since this study was not designed to test the effect of treatment on these symptoms, further studies may be needed to confirm these results.

What medical problems did the study participants have?

Side effects are medical problems (such as feeling tired) that happened during the study which the study doctor thought could be related to the treatments in the study. This section provides a summary of side effects related to the study drug. 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, involve significant disability, or require hospitalization. Some participants stop study treatment because of side effects.

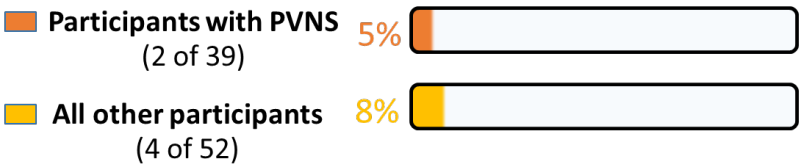
How many participants had serious side effects?

In Part 1, side effects were monitored for 41 participants. 5% (2 of 41) of participants reported serious side effects.

- 1 participant had increased risk of bleeding in the PLX3397 300 mg/day group.
- 1 participant in the PLX3397 1200 mg/day group had low number of red blood cells, low neutrophil count, and fainting. Neutrophils are a type of white blood cell that help fight infection.

In Part 2, side effects were monitored for 91 participants and are presented below.

Percentage of participants who had serious side effects during Part 2



Participants with PVNS	Serious side effects	All other participants
0%	Bleeding in liver	2% (1 of 52)
0%	Brain stroke	2% (1 of 52)
0%	Decreased oxygen supply	2% (1 of 52)
0%	Fever in participants with low neutrophils	2% (1 of 52)
3% (1 of 39)	Increase in liver test value of transaminase in the blood	0%
3% (1 of 39)	Low sodium level in blood	0%
0%	Lung infection	2% (1 of 52)

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

1 participant in the 'All other participants' group of Part 2 died due to brain stroke.

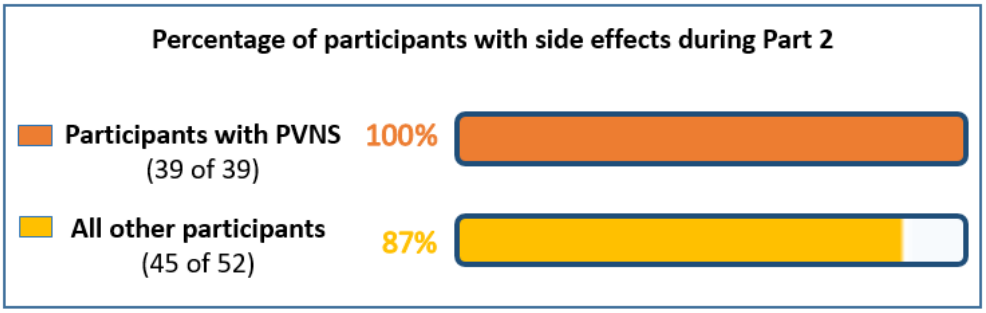
What were the most common side effects?

The most common side effects, both serious and non-serious, reported by at least 10% (10 of 100) of participants in any group during Part 1 are presented below.

Most common side effects reported during Part 1

Side effects	200 mg 3 participants	300 mg 6 participants	400 mg 6 participants	600 mg 6 participants	900 mg 7 participants	1000 mg 7 participants	1200 mg 6 participants
Decreased appetite	0	0	0	17% (1 of 6)	14% (1 of 7)	57% (4 of 7)	33% (2 of 6)
Feeling tired	0	33% (2 of 6)	0	0	57% (4 of 7)	14% (1 of 7)	17% (1 of 6)
Feeling sick to your stomach	33% (1 of 3)	0	17% (1 of 6)	33% (2 of 6)	57% (4 of 7)	29% (2 of 7)	33% (2 of 6)
Hair color changes	0	0	0	17% (1 of 6)	29% (2 of 7)	43% (3 of 7)	33% (2 of 6)
Low number of red blood cells	0	17% (1 of 6)	17% (1 of 6)	33% (2 of 6)	29% (2 of 7)	14% (1 of 7)	33% (2 of 6)
Vomiting	0	0	17% (1 of 6)	17% (1 of 6)	14% (1 of 7)	29% (2 of 7)	17% (1 of 6)

The most common side effects, both serious and non-serious, reported by at least 10% (10 of 100) of participants in any group during Part 2 are presented below.



Most common side effects reported during Part 2

Participants with PVNS	Most common side effects	All other participants
74% (29 of 39)	Feeling tired	40% (21 of 52)
72% (28 of 39)	Hair color changes	31% (16 of 52)
56% (22 of 39)	Feeling sick to your stomach	33% (17 of 52)
39% (15 of 39)	Swelling around the eyes	6% (3 of 52)
36% (14 of 39)	Altered sense of taste	12% (6 of 52)
31% (12 of 39)	Itching	6% (3 of 52)
23% (9 of 39)	Diarrhea	17% (9 of 52)
23% (9 of 39)	Low phosphate level in blood	6% (3 of 52)
23% (9 of 39)	Rash	8% (4 of 52)
21% (8 of 39)	Decreased appetite	39% (20 of 52)
21% (8 of 39)	Headache	2% (1 of 52)
21% (8 of 39)	Vomiting	19% (10 of 52)
18% (7 of 39)	Condition that affects learning, memory, & perception of time	0%
18% (7 of 39)	Increase in liver test value of alanine aminotransferase in the blood	6% (3 of 52)
18% (7 of 39)	Increase in liver test value of aspartate aminotransferase in the blood	8% (4 of 52)
18% (7 of 39)	Raised red bumps on the skin	2% (1 of 52)
18% (7 of 39)	Swelling in lower legs and hands	4% (2 of 52)
15% (6 of 39)	Facial swelling	4% (2 of 52)

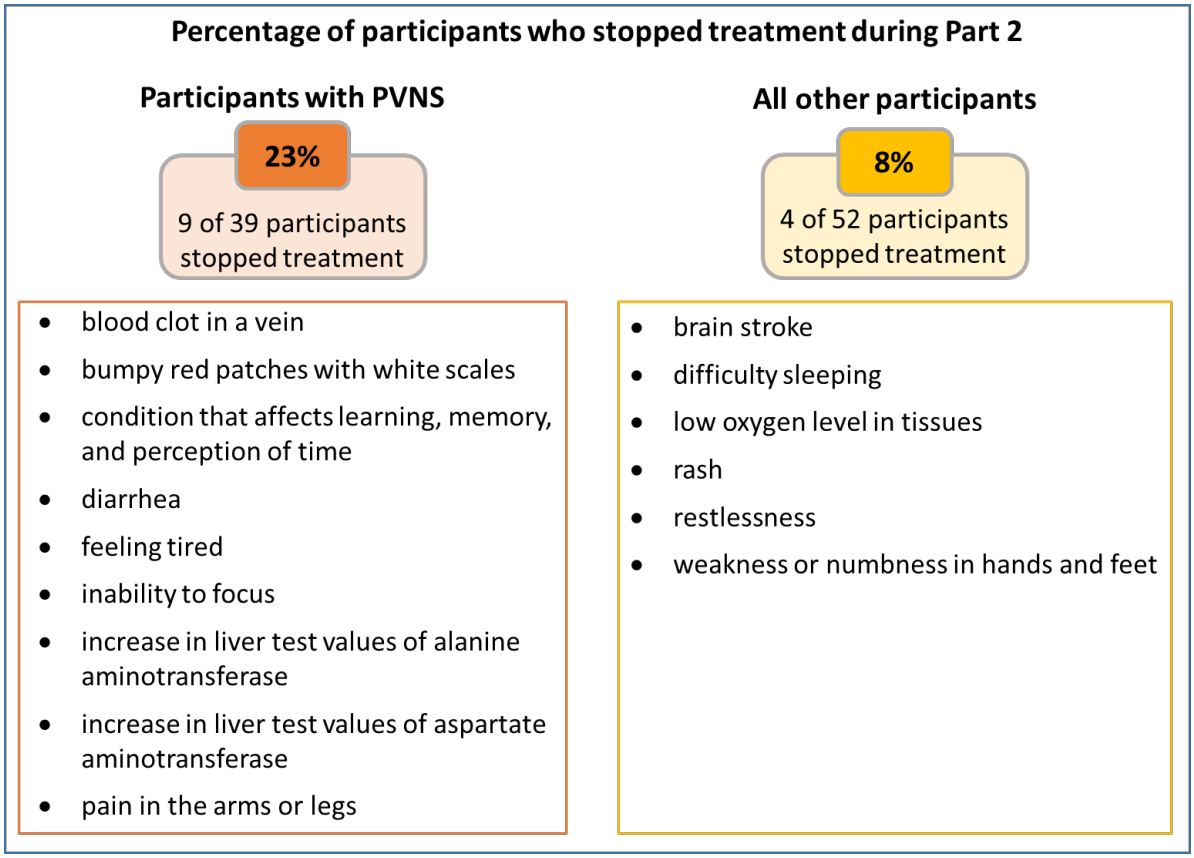
Most common side effects reported during Part 2

Participants with PVNS	Most common side effects	All other participants
15% (6 of 39)	Low number of red blood cells	10% (5 of 52)
15% (6 of 39)	Patches of skin lighter than overall skin tone	4% (2 of 52)
13% (5 of 39)	Dry skin	0%
13% (5 of 39)	Inflammation of the inner lining of the body and its organs	4% (2 of 52)
10% (4 of 39)	Acid reflux	0%
10% (4 of 39)	Dry mouth	4% (2 of 52)
10% (4 of 39)	Difficulty sleeping	14% (7 of 52)
10% (4 of 39)	Feeling dizzy	0%
10% (4 of 39)	High blood pressure	2% (1 of 52)
10% (4 of 39)	Increase in liver test value of alkaline phosphatase in the blood	2% (1 of 52)
10% (4 of 39)	Indigestion	0%
10% (4 of 39)	Impaired memory	0%
10% (4 of 39)	Joint pain	0%
10% (4 of 39)	Weight increased	0%

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

In Part 1, 7% (3 of 41) of participants stopped study treatment early because of side effects. The side effects that led to participants stopping study treatment were low lymphocyte count and increase in liver test value of aspartate aminotransferase in the blood. Lymphocytes are a type of white blood cell that help fight infection.

In Part 2, 12% (11 of 91) of participants stopped treatment early because of side effects. The side effects that led to participants stopping study treatment are provided below.



How was this study useful for patients and researchers?

This study helped researchers learn if PLX3397 can reduce the growth of tumor cells. This study also helped researchers learn about the safety and other effects of PLX3397 when given to participants with different types of tumor.

Other studies of PLX3397 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 NCT01004861 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 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Patients with Advanced, Incurable, Solid Tumors in which the Target Kinases Are Linked to Disease Pathophysiology.

Sponsor: Daiichi Sankyo, Inc.

Sponsor contact information:
211 Mount Airy Road, Basking Ridge, NJ 07920
Email: CTRInfo@dsi.com
Phone number: 1-908-992-6640

Date of this summary: 02 December 2020

This summary was prepared by Kinapse, a Syneos Health® company.