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Clinical Trial Summary

Ivosidenib, Nivolumab, and Ipilimumab Combination in Previously Treated Subjects with Nonresectable or Metastatic IDH1-Mutant Cholangiocarcinoma

Full scientific title: A Phase 1/2, Safety Lead-in and Dose Expansion, Open-label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Activity of Ivosidenib in Combination with Nivolumab and Ipilimumab in Previously Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation

We thank all the participants who took part in the study. Clinical study participants are very important for making progress in science, for the benefit of patients.
This document is a summary of the study. It is written for a general audience.

Researchers need many studies to decide which medicines work the best and are the safest for patients. For medical science to progress, many studies involving patients are running all around the world. This summary only shows the results from this one study. Other studies, evaluating the same drug, may find different results. You should not change your current treatment based on the results of this study. If you have any questions about this study, please talk to your doctor.

Therapeutic area:
Oncology

Disease:
Cholangio-carcinoma

Study phase:
Phase 1/2

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Clinical Trial Summary

Ivosidenib, Nivolumab, and Ipilimumab Combination in Previously Treated Subjects with Nonresectable or Metastatic IDH1-Mutant Cholangiocarcinoma

1 Why was this study done?

This study was done to test a cancer drug called ivosidenib (also called S095031 or AG-120) in combination with nivolumab and ipilimumab. The study involved participants with a type of advanced bile duct cancer called cholangiocarcinoma whose cancer cells had a change (mutation) in the isocitrate dehydrogenase 1 (IDH1) gene.

In several types of cancer such as cholangiocarcinoma, an abnormal form of a protein IDH1 is present in the tumor cells due to changes called mutations. When IDH1 is mutated, it produces too much 2-hydroxyglutarate (2-HG), which is a substance that is normally present in cells in low levels. Too much 2-HG can change how normal cells function and may cause them to become tumor cells.

Ivosidenib is a drug that blocks the activity of abnormal IDH1 proteins and reduces 2-HG levels in tumor cells to normal levels. Ivosidenib is already available to treat cholangiocarcinoma and certain blood cancers in some countries.

In this study, ivosidenib was combined with nivolumab and ipilimumab. These 2 medicines are immune check point inhibitors that help the immune system kill cancer cells. They are available in some countries to treat various types of tumors. Researchers hoped that using ivosidenib with nivolumab and ipilimumab will work better than using ivosidenib alone.

The study had 2 parts. The main objectives of this study were:

- Part 1: to assess the safety of ivosidenib in combination with nivolumab and ipilimumab and to find the recommended dose of ivosidenib (the one that is both safe and effective for patients) when given in combination with nivolumab and ipilimumab.
- Part 2: to see how well ivosidenib works in combination with nivolumab and ipilimumab.

2 When and where did this study take place?

When did the study take place?

- This study started in October 2023.
- It ended in November 2024.

Where did the study take place?

The study took place in the following countries:

Country	Number of participants
United Kingdom	2
United States of America	5

3 Who participated in the study?

Which participants were included in the study?

Participants were included in the study if they:

- Were at least 18 years old.
- Had cholangiocarcinoma:
  - with IDH1 mutation.
  - that could not be removed by surgery (nonresectable) or had spread to other parts of the body (metastatic).
- Had taken up to 2 different anticancer treatments before, that did not work, or they could not tolerate.
- Had good blood, kidney and liver function.

Participants were not included in the study if they had:

- Already taken medicines that block the activity of IDH proteins.
- Any major surgery within 4 weeks of starting the study or had not recovered after surgery.

How many participants took part in the study?

A total of 7 participants took part in the study. All were female.

The second part of the study did not take place because the study was stopped during the first part (see explanations in section 7 of this summary).

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How old were the participants?

The average age of the participants was 56 years. The youngest participant was 32 years old and the oldest was 81 years old.

4 Which treatments did the participants receive?

Participants received ivosidenib in combination with nivolumab and ipilimumab as:

- **Ivosidenib** was taken as tablets by mouth once a day during time periods called "cycles". Each cycle consisted of 21 days for the first 4 cycles. The length of the cycle was increased to 28 days from Cycle 5. Cycles of treatment were repeated for as long as the cancer did not progress (get worse) and if the participant did not have side effects that were too severe. Participants could also decide to stop the treatment at any time without giving a reason.

  Participants took ivosidenib at daily doses of 500 mg (2 tablets) or 250 mg (1 tablet).

- **Nivolumab** was given through infusion (an injection given slowly, over 30 minutes) into a vein once every 3 weeks in each cycle of treatment. Each cycle consisted of 21 days for the first four cycles. The length of the cycle was increased to 28 days from Cycle 5. Cycles of treatment were repeated for as long as the cancer did not progress or for a total duration of 24 months.

  Participants received nivolumab at a dose of 3 mg per kilogram (mg/kg) of body weight every 3 weeks. Starting at Cycle 5, the dose was changed to 480 mg every 4 weeks.

- **Ipilimumab** was given through infusion over 30 minutes into a vein every 3 weeks in each cycle of treatment for the first four cycles only. Each cycle was of 21 days. Participants received ipilimumab at a dose of 1 mg/kg of body weight every 3 weeks for four cycles.

5 How was the study carried out?

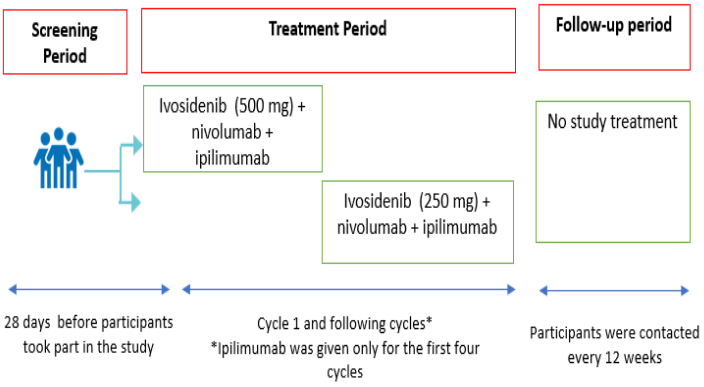
The study is called an "open-label" study. This means that both the participants and the research doctors knew which treatment was given.

The study started with a screening period, which lasted up to 28 days. During this time, doctors checked if people who wanted to enter the study met all the necessary requirements.

After the screening period, participants entered the treatment period.

Once the treatment ended, participants had a follow-up period (up to 2 years after the last dose of study drug). During this period, participants were contacted every 12 weeks to check on their health and well-being.

The study design is presented in the image below.



To find the recommended dose of ivosidenib to use in combination with nivolumab and ipilimumab, the doctors first tested ivosidenib at the dose of 500 mg in combination with nivolumab and ipilimumab in a small group of participants. After reviewing the side effects from this group, the study did not continue with the 500 mg dose of ivosidenib, and a second group was opened to test the 250 mg dose.

For each dose, the doctors closely checked the safety of the study drugs.

The participants visited the doctors regularly. During the visits, the doctors collected information about the participants' health.

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6 What were the side effects?

Side effects are unwanted medical events that the doctors think may be caused by the treatments in the study.

In this summary, we describe unwanted medical events thought to be caused by ivosidenib, nivolumab or ipilimumab.

The results may be presented differently in other documents related to the study.

The table below shows the number of participants who had side effects.

	Ivosidenib 500 mg + nivolumab + ipilimumab (out of 4 participants)	Ivosidenib 250 mg + nivolumab + ipilimumab (out of 3 participants)
Participants who had side effect(s)	4 (100%)	3 (100%)
Participants who had serious* side effect(s)	2 (50%)	2 (67%)
Participants who stopped the treatment because of side effect(s)	2 (50%)	1 (33%)

**See definition of serious side effects below*

What were the types of side effects?

The table below shows the most common side effects reported in the study (reported by at least 2 participants in either treatment group).

	Ivosidenib 500 mg + nivolumab + ipilimumab (out of 4 participants)	Ivosidenib 250 mg + nivolumab + ipilimumab (out of 3 participants)
Skin rash due to overactivity of the immune system (the body system and its cells that fight diseases)	4 (100%)	3 (100%)
Tiredness	4 (100%)	1 (33%)
Diarrhoea	3 (75%)	1 (33%)
Itching	3 (75%)	0
Difficulty in breathing	2 (50%)	1 (33%)
Feeling sick	2 (50%)	1 (33%)
Fever	2 (50%)	1 (33%)
Lower appetite	2 (50%)	0
Dry mouth	2 (50%)	0
Taste changed	2 (50%)	0

= *participants*

What were the serious side effects?

A side effect is considered serious when:

- the participant needs to be hospitalised,
- it causes lasting damage or death,
- the participant's life is in danger or,
- it is medically important in the doctor's opinion.

The table below shows the serious side effects reported in this study.

	Ivosidenib 500 mg + nivolumab + ipilimumab (out of 4 participants)	Ivosidenib 250 mg + nivolumab + ipilimumab (out of 3 participants)
Skin rash due to overactivity of the immune system (the body system and its cells that fight diseases)	1 (25%)	2 (67%)
Inflammation of the liver caused by overactivity of the immune system (the body system and its cells that fight diseases)	1 (25%)	0
Fever	1 (25%)	0

= *participants*

In the study, no participants died because of an unwanted event thought to be caused by ivosidenib, nivolumab and ipilimumab.

7 What were the study results?

The study was stopped earlier than planned. The sponsor (the company that organised and funded the research) stopped enrolment of new participants in Part 1 because all participants enrolled in the study developed skin rash due to overactivity of the immune system and with no visible improvements seen in tumors. As a result, the Part 2 of the study was not conducted.

This document presents only the results for the main goal of the study from Part 1. Other results are available in other documents listed in section 10.

Due to the early end of the study and the small number of participants who took part in the study, most of the main objectives could not be met. As a result, there was not enough information for researchers to make any strong conclusions.

The side effects of ivosidenib in combination with nivolumab and ipilimumab are described in section 6 of this summary.

8 How has this study helped research?

The study helped researchers gather more information on the safety of the ivosidenib in combination with nivolumab and ipilimumab. This study also helped researchers better understand how these medicines work in treating cholangiocarcinoma.

This summary shows only the main results from this one study. Other studies, evaluating the same drugs, may find different results.

9 Are there plans for further studies?

Clinical studies with ivosidenib are on-going and further studies are planned.

10 Further information

What are the identification numbers of the study?

- Protocol code: CL1-95031-006
- US NCT number: NCT05921760

Who did the study?

The company that organised and funded the research, called the "sponsor", is the Institut de Recherches Internationales Servier based in Gif-Sur-Yvette, France.

How can you contact the sponsor?

Contact us on the Servier website https://servier.com/en/.

Where can you learn more about this study?

You can find more information about this study on these websites:

- https://clinicaltrials.servier.com/find-clinical-trials/
- http://www.clinicaltrials.gov/

In this document we translated medical terms into lay terms. You can find the corresponding medical terms in the Servier glossary at https://clinicaltrials.servier.com/glossary/

You can find general information about clinical trials on https://clinicaltrials.servier.com/