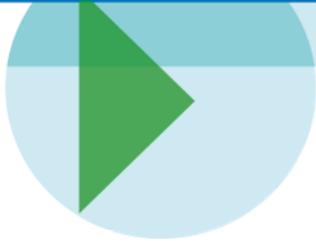


Protocol Summary

of Clinical Trial



The protocol of a clinical study is a document that explains why and how a study will be carried out.

Ivosidenib Plus Durvalumab and Gemcitabine/Cisplatin as First-Line Therapy in Participants with Locally Advanced or Metastatic Cholangiocarcinoma with an IDH1 Mutation

Full scientific title: A Phase 1b/2, Safety Lead-in and Dose-Expansion, Open label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Activity of Ivosidenib in Combination with Durvalumab and Gemcitabine/Cisplatin as First-line Therapy in Participants with Locally Advanced, Unresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation (EU Study Number: 2024-514261-19-00)

1 Why is this study needed?

This study is done to test a drug called ivosidenib in combination with durvalumab and gemcitabine/cisplatin in participants with a type of severe bile duct cancer (cholangiocarcinoma) that cannot be treated with surgery. Bile ducts are tiny tubes carrying bile from the liver to the intestine. Bile helps to digest fats in food. In several types of cancer such as cholangiocarcinoma, an abnormal (mutated) form of a protein called isocitrate dehydrogenase 1 (IDH1) is present in the tumor cells due to gene changes called mutations. This leads to the overproduction of 2-hydroxyglutarate (2-HG), a substance that is normally present in cells at low levels. Too much 2-HG impairs normal cell functioning and may cause them to become tumor cells.

Ivosidenib is a drug that blocks the activity of abnormal IDH1 proteins, which reduces 2-HG levels in tumor cells back to normal levels.

Researchers believe that combining ivosidenib with other approved treatments called durvalumab and gemcitabine/cisplatin might help treat these cancers better and improve the lives of people who have them.

2 What are we mainly looking for?

What is the main goal of the study?

The main goals of this study are:

Part 1:

- To look at the safety and tolerability of ivosidenib in combination with durvalumab and gemcitabine/cisplatin and to find the best (recommended) dose for this combination.

Part 2:

- To see how well ivosidenib in combination with durvalumab and gemcitabine/cisplatin works in treating the tumor.

What is (are) the main study endpoint(s)?

A study endpoint is the measurement used to decide whether a study goal is reached or not. The main endpoints of this study are:

Part 1:

- The number and type of dose-limiting toxicities (DLT) during the first 21 days of treatment. A DLT is a side effect that is severe enough to not continue treatment with the study drug(s). Side effects are unwanted medical events that the doctors think may be caused by the study treatment(s).
- The number of unwanted medical events that occur during Part 1 and how serious they are.
- Changes in the dose and schedule of study drugs by monitoring how often the dose needs to be reduced, delayed, paused, or stopped completely.

Part 2:

- The percentage of patients whose cancer shrinks or disappears after treatment, known as the objective response (OR).

3 What about the other goals of the study?

What are the other goals of this study?

The other goals of this study are:

- To understand how the body processes (absorbs, distributes, and removes) ivosidenib when given in combination with durvalumab and gemcitabine/cisplatin. Scientists call this pharmacokinetics (PK).
- To study the effect of ivosidenib in combination with durvalumab and gemcitabine/cisplatin on the body, which is called pharmacodynamics (PD).
- To study how the body's immune system (defense system) responds to durvalumab.
- To look at the safety and tolerability of the recommended dose of ivosidenib (dose selected in Part 1) in combination with durvalumab and gemcitabine/cisplatin in Part 2.

What are the other study endpoints?

The other study endpoints are:

- PK assessments, including levels of ivosidenib in the blood at different times, the highest level of ivosidenib in the blood and the time taken to achieve it, and the total measure of ivosidenib in the blood over a period of time.
- PD assessment, including measuring how much 2-HG is found in the participants' blood at different timepoints.
- The level of a protein (antibody) produced by the immune system against durvalumab.
- The number of unwanted medical events that occur during Part 2 and how serious they are.
- Changes in the size of the tumors, how quickly the tumor shrinks or disappears, and how long it remains smaller or gone.
- How long participants live after the start of the treatment and how long they live without their cancer getting worse.
- Changes in the dose and schedule of study drugs in Part 2 by monitoring how often the dose needs to be reduced, delayed, paused, or stopped completely.

4 Who is participating in the study?

Overall, about 52 participants are expected in the study.

To take part, participants have to:

- Be adults aged 18 or older.
- Have a documented IDH1 mutation in their tumor.
- Have cholangiocarcinoma that has spread to nearby areas (locally advanced) or other organs (metastatic) in the body and cannot be removed by surgery.
- Have adequate bone marrow (the spongy tissue inside bones where blood cells are made), liver, and kidney function.

5 How is the study carried out?

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

The study has two parts. In Part 1, a small number of participants will receive ivosidenib in combination with durvalumab and gemcitabine/cisplatin to assess the safety and tolerability of the combination and to determine the recommended dose of ivosidenib when given in combination. This part is called the safety lead-in phase.

After the Part 1 is finished, Part 2 of the study will evaluate the recommended dose of ivosidenib found in Part 1 in combination with durvalumab and gemcitabine/cisplatin in other participants to better determine the safety and effectiveness of the combination. This part is called the expansion phase.

6 What are the treatments and tests used in the study?

In Part 1, participants will take ivosidenib tablets by mouth at a dose of 500 mg or 250 mg once a day. Participants will also receive 1500 mg of durvalumab every three weeks and gemcitabine (1000 mg/m²)/cisplatin (25 mg/m²) on Day 1 and Day 8 through a drip into a vein. The drugs will be taken during periods called "cycles". The first 8 cycles will last 21 days. From Cycle 9, participants will take ivosidenib once daily and durvalumab will be given once every four weeks during a 28-day cycle. These cycles will be repeated for as long as the

cancer does not progress and the participant does not have side effects that are too severe. The participant can also decide to stop the treatment at any time.

In Part 2, participants will take ivosidenib at a recommended dose as tablets by mouth. Participants will also receive durvalumab and gemcitabine/cisplatin through a drip into a vein, like in Part 1.

7

What are the possible benefits and risks?

The participant's disease may or may not improve with the study treatment. Participants will receive close medical follow-up.

The results of this study will help the researchers learn more about the study drugs. Studies such as this one could lead to better treatments for people with similar medical conditions in the future.

Researchers designed the study to be safe, with minimal risk or discomfort for participants. The study has strict safety rules and regular check-ups. As with all medicines, ivosidenib with durvalumab and gemcitabine/cisplatin treatment may cause side effects. Every care will be taken to avoid and treat side effects if they occur.

The study doctors will tell the participants about the known and possible risks and side effects of ivosidenib, durvalumab, gemcitabine, and cisplatin. Before enrolling in the study, participants will be provided with an informed consent document, and they will have the opportunity to ask questions and discuss any concerns with their healthcare provider. The informed consent document will contain detailed information on benefits, risks, and side effects. This is a document that provides people with the information they need to decide if they want to join the study.