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.

Vorasidenib and Pembrolizumab Combination in Recurrent or Progressive IDH-1 Mutant Glioma

Full scientific title: *A Phase 1, Safety Lead-In and Randomized, Open-label, Perioperative Study of Vorasidenib in Combination with Pembrolizumab in Subjects with Recurrent or Progressive IDH-1 Mutant Glioma.*

1 Why is this study needed?

This study is needed to find better treatments for a type of brain cancer called glioma in people whose tumor may have come back after surgery (called recurrent) or is getting worse (called progressive) despite treatment. In some gliomas, an abnormal (mutated) form of a protein called isocitrate dehydrogenase (IDH) 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 some brain cells to become tumor cells.
Vorasidenib is a medicine that blocks the activity of abnormal IDH proteins. Vorasidenib may also increase the presence of immune cells in brain tumors. Pembrolizumab is another medicine that helps the immune system fight cancer.
Researchers believe that combining vorasidenib and pembrolizumab might help treat these recurrent/progressive tumors better compared to when these medicines are used alone.

2 What are we mainly looking for?

What is the main goal of the study?

The main goals of this study are:

- To look at the safety and tolerability of vorasidenib in combination with pembrolizumab, and to find the best dose for this combination.
- To see if the combination of vorasidenib and pembrolizumab increases the presence of CD3+ T-cells (a type of immune cell) in tumors compared with untreated tumors.

What are the main study endpoints?

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

- 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 prevent an increase in dose of 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 the study and how serious they are.
- The number of CD3+ T-cells (a type of immune cell) present in surgically removed tumors after treatment with vorasidenib and pembrolizumab compared to untreated tumors.

3 What about the other goals of the study?

What are the other goals of this study?

- To further see how well vorasidenib in combination with pembrolizumab works in controlling the tumor growth.
- To understand how the body processes vorasidenib alone or in combination with pembrolizumab. Scientists call this pharmacokinetics (PK).

- To measure the level of 2-HG in surgically removed tumors after being treated with either vorasidenib alone or with pembrolizumab, compared with untreated tumors.
- To check how many CD3+ T-cells are present in surgically removed tumors after treatment with vorasidenib and pembrolizumab, compared to tumors treated with vorasidenib alone.

What are the other study endpoints?

Other study endpoints include:

- The percentage of patients whose cancer shrinks or disappears after treatment, known as the overall response.
- 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.
- The number of participants whose cancer has not worsened 6 months after their first dose.
- PK measurements, including levels of vorasidenib alone or in combination with pembrolizumab in the blood and tumors at different times.
- The level of 2-HG and number of CD3+ T-cells in surgically removed tumors.

4 Who is participating in the study?

About 66 to 72 participants are expected in the study.

To take part, participants have to:

- Be adults aged 18 years or older.
- Have recurrent or progressive glioma with a documented IDH1 mutation.
- Have previously received treatment with chemotherapy (treatment with medications directed towards their cancer), radiation, or both.
- Have been recommended to undergo surgery as treatment of glioma for participants in Part 2 (see more details below).
- Have adequate organ and bone marrow 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 different doses of vorasidenib in combination with a standard dose of pembrolizumab to determine the best and safest combination dose. This part is called the safety lead-in phase.

After the Part 1 is finished, Part 2 of the study will evaluate the best dose of the combination found in Part 1 in at least 60 additional participants before their planned surgery. This part is called the randomized perioperative phase. Randomized means that the participants are put by chance into one of 3 groups: one receives vorasidenib alone, one receives vorasidenib (at the best dose) in combination with pembrolizumab, and one group receives no treatment prior to surgery. The assigned treatment will be given for about a month before surgery. After patients have recovered from surgery, all patients will have the option to take vorasidenib in combination with pembrolizumab.

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

Participants will take vorasidenib as tablets by mouth and pembrolizumab 200 mg will be given through a drip into a vein. The drugs will be taken during periods called "cycles".

In Part 1, one cycle will last 21 days. Participants will receive vorasidenib daily and pembrolizumab on Day 1 of each cycle. These 21-day cycles will be repeated for as long as the cancer does not progress, and the participant does not have too severe side effects. The participant can also decide to stop the treatment at any time.

In Part 2, one cycle will last 28 days. Participants will take vorasidenib daily for 28 days, including the day of their surgery.

Some participants will also receive pembrolizumab, along with vorasidenib. Pembrolizumab will be given through a drip into a vein on Day 1 and Day 22 during this 28-day cycle.

Participants can also choose to receive vorasidenib in combination with pembrolizumab after the surgery.

Participants will visit the study doctors regularly for check-ups to closely monitor the safety of the study treatments and how well they work. These check-ups will include blood and urine tests, scans to look at the tumors, monitoring of side effects and other health checks.

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, vorasidenib and pembrolizumab 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 vorasidenib and pembrolizumab.

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 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.