Title: A Phase 1 Study of ALN-BCAT as Monotherapy and in Combination with Pembrolizumab in Patients With Advanced or Metastatic Hepatocellular Carcinoma

Brief Title: A Study to Evaluate ALN-BCAT in Patients With Hepatocellular Carcinoma

EU Trial Number: 2024-519499-22

WHY IS THIS RESEARCH NEEDED?

Hepatocellular Carcinoma (**HCC**) is a type of liver cancer commonly caused by other liver problems like hepatitis B or C virus infection, alcoholic liver disease, or fatty liver disease. For more than half of the people with HCC, the cancer is advanced or has spread from its original location to other parts of the body (called **metastatic**). Metastatic means the cancer has become harder to treat with surgery or other medicines that target the tumor.

Researchers are testing a new medicine, **ALN-BCAT**, for people with advanced or metastatic HCC. ALN-BCAT works differently than current medicines. It targets a gene in the body (called **CTNNB1**) that directs cells using instructions, or **mRNA**, to make a protein called **beta-catenin.** People with HCC often have too much beta-catenin. Researchers are testing whether ALN-BCAT can decrease the level of beta-catenin and slow down or stop tumor growth. The study will also check to see if ALN-BCAT works better when given with another medicine (called **pembrolizumab**) that is used to help the immune system fight cancer**.**

WHAT ARE THE GOALS OF THIS STUDY AND HOW WILL THEY BE MEASURED?

Researchers are testing ALN-BCAT two ways: given by itself (**monotherapy**) and given with pembrolizumab (**combination therapy**). The **dose escalation** part will test what dose amount is safe and if ALN-BCAT is able to shrink tumors in participants with HCC. The main goal of dose escalation is to start with a low dose and increase the dose until doctors can find 1 or 2 recommended doses. The **dose expansion** part of the study will test the recommended doses on a different group of participants with HCC.

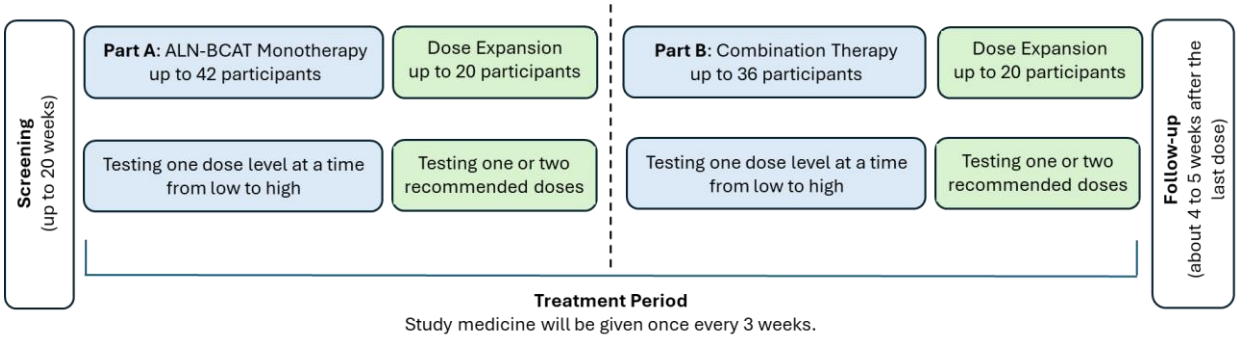
Goals for the Dose Escalation Part of the Study	How Researchers Measure the Goals
Primary	
To find out which doses of ALN-BCAT are safe when given alone or with pembrolizumab.	• Record all the medical problems, called **adverse events** that happen to participants while they are in the study.
To determine the most effective doses of ALN-BCAT to use alone or with pembrolizumab.	• Record any severe adverse events that limit how much ALN-BCAT can be given. • Measure the ability of ALN-BCAT to stop or slow tumor growth. • Study how ALN-BCAT acts in the body.
Secondary	
To see how ALN-BCAT moves through and out of the body.	• Measure the amount of ALN-BCAT in the blood and how long it takes to reach the highest level.
To check if ALN-BCAT is affecting the process by which the CTNNB1 gene is instructing cells in the body to produce beta-catenin protein.	• Record the percent change in mRNA levels from tumor samples taken before and during treatment.
To see how well ALN-BCAT works against the cancer when given alone or with pembrolizumab.	• Measure the effectiveness of ALN-BCAT to improve the amount and duration of tumor shrinkage.

WHO CAN TAKE PART IN THE STUDY?

This study includes up to 158 adults with advanced or metastatic liver cancer that became worse after treatment. Participants in this study will be healthy enough to do normal daily activities with little help. The study will have about 25 locations in the United States, Europe, and maybe other countries.

HOW IS THE STUDY DESIGNED?

The dose escalation has 2 main parts. During **Part A**, ALN-BCAT is given as monotherapy. During **Part B**, ALN-BCAT is given with pembrolizumab as combination therapy. In each part of the dose escalation, different doses (from low to high) of study medicine are given to a small number of participants, one group at a time. Once a recommended dose is available from Part A and Part B, the study sites will enroll up to 20 new participants for the dose expansion. Study medicine is given every 3 weeks until the cancer gets worse or participants have too many severe medical problems (called adverse events). The duration of the study will be different for each participant. Throughout the study, doctors will monitor participants' health, perform scans to assess tumor response, and collect blood and tumor samples to learn how the medicine works in the body.



HOW WILL THE STUDY MEDICATION BE GIVEN?

Study medicine will be given within a vein as an **intravenous infusion**.

WHAT RISKS AND BENEFITS WILL PARTICIPANTS EXPERIENCE?

ALN-BCAT may help treat advanced liver cancer, but it is not certain if participants in this study will benefit. Possible medical problems include infusion reactions, liver problems, and nerve issues. Study doctors will monitor participants for any adverse events during the study. More information on the benefits and risks is available in the protocol.

WHERE CAN I LEARN MORE ABOUT THE STUDY?

For more details on this study please speak with a doctor, or visit:
https://euclinicaltrials.eu/ Use the study identifier **2024-519499-22**