ForPatients
by Roche

Non-Small Cell Lung Cancer (NSCLC)Non Small Cell Lung Carcinoma

A study to compare divarasib with sotorasib or adagrasib in people with KRAS G12C-positive non-small cell lung cancer that has previously been treated and has either spread or has no other treatments available for it

A Study Evaluating the Efficacy and Safety of Divarasib Versus Sotorasib or Adagrasib in Participants With Previously Treated KRAS G12C-positive Advanced or Metastatic Non-Small Cell Lung Cancer

Trial Status	Trial Runs In	Trial Identifier
Recruiting	25 Countries	NCT06497556 2024-510908-37-00 BO45217

The information is taken directly from public registry websites such as ClinicalTrials.gov, EuClinicalTrials.eu, ISRCTN.com, etc., and has not been edited.

Official Title:

A Phase III, Randomized, Open-Label, Multicenter Study Evaluating the Efficacy and Safety of Divarasib Versus Sotorasib or Adagrasib in Patients With Previously Treated KRAS G12C-Positive Advanced or Metastatic Non-Small Cell Lung Cancer

Trial Summary:

The purpose of this study is to assess the safety and efficacy of divarasib compared to locally approved KRAS G12C inhibitors (sotorasib or adagrasib) in participants with KRAS G12C-positive (KRAS G12C +) advanced or metastatic non-small cell lung cancer (NSCLC).

Hoffmann-La Roche Sponsor	**Phase 3** Phase

NCT06497556 2024-510908-37-00 BO45217
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	#18 Years	No

1. Why is this study needed?

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. NSCLC usually develops in the tissues lining the lungs and can spread to nearby lymph nodes and other organs. Standard treatment for NSCLC is chemotherapy, immunotherapy, or both. Chemotherapy kills cancer cells directly. Immunotherapy is a type of medicine that helps a person's own immune system attack cancer cells. But some cancers have a certain change in a gene (a section of DNA that has instructions for making the body) called *KRAS*. –. KRAS proteins are involved in normal cell survival and growth. When cancers have a change in the *KRAS* gene (known as ' *KRAS G12C*-positive'), the KRAS proteins keep cancer cells alive and make them grow faster. Better treatments are needed for *KRAS G12C*-positive NSCLC.

The U.S. Food and Drug Administration and European Medicines Agency are types of health authorities. Sotorasib and adagrasib are approved by health authorities on their own for the treatment of *KRAS G12C*-positive NSCLC in some countries. This study is testing a medicine called divarasib. It is being developed to treat *KRAS G12C*-positive NSCLC. Divarasib is an experimental medicine. This means health authorities have not approved divarasib for the treatment of *KRAS G12C*-positive NSCLC that has spread, or has no other standard treatments available for it.

This study aims to compare the effects of divarasib versus sotorasib or adagrasib. But only in people with *KRAS G12C*-positive NSCLC that has previously been treated. And that has spread or has no other treatments available for it.

2. Who can take part in the study?

People of 18 years of age or older with *KRAS G12C*-positive NSCLC can take part in the study. But only if their cancer has gotten worse after 1 to 3 previous treatments. And if their cancer has spread or has no other treatments available for it.

People may not be able to take part in this study if they have had prior treatment that targets KRAS proteins. People who cannot swallow tablets will not be able to take part. People who are pregnant, or currently breastfeeding cannot take part in the study.

3. How does this study work?

Participants will be screened to check if they are able to participate in the study. The screening period will take place from 1 day to 1 month before the start of treatment.

Everyone who joins this study will be placed into 1 of 2 groups randomly (like flipping a coin) and given either:

- **Group 1:** divarasib given as a tablet to be swallowed daily

- **Group 2:** sotorasib given as a tablet to be swallowed daily OR adagrasib given as a tablet to be swallowed twice a day

Participants will have an equal chance of being placed in either group. The treatment given to participants in Group 2 will depend on which treatments are available at their study centre. And the participants' and study doctor's decision if both treatments are available. This is an open-label study. This means everyone involved, including the participant and the study doctor, will know the study treatment the participant has been given.

During this study, the study doctor will see participants around 4 times during the first 6 weeks. Then once every 3 weeks. They will see how well the treatment is working and any unwanted effects participants may have. Participants will have follow-up visits once every 6 weeks after completing the study treatment until their cancer gets worse. Then once every 3 months for as long as they agree to it. The study doctor will check on the participant's well being. Total time of participation in the study could be more than 4 years. Participants have the right to stop study treatment and leave the study at any time, if they wish to do so.

4. What are the main results measured in this study?

The main result measured in the study to assess if the medicines have worked is how long people live without their cancer getting worse.

Other key results measured in the study include:

- How long people live
- The duration it takes for a person to experience a significant worsening in measures such as chest pain, cough, difficulty breathing, quality of life, or the ability to perform daily activities
- How many people have a positive response to the treatment
- How much time there is between the participant's cancer first responding to treatment and the cancer getting worse
- The number and seriousness of unwanted effects
- How much certain symptoms or unwanted effects (such as cough, chest pain and difficulty breathing) change compared with the start of the trial
- How often participants report that unwanted effects impact their daily life and their ability to function and enjoy life

5. Are there any risks or benefits in taking part in this study?

Taking part in the study may or may not make participants feel better. But the information collected in the study can help other people with similar health conditions in the future.

It may not be fully known at the time of the study how safe and how well the study treatment works. The study involves some risks to the participant. But these risks are

generally not greater than those related to routine medical care or the natural progression of the health condition. People interested in taking part will be informed about the risks and benefits, as well as any additional procedures or tests they may need to undergo. All details of the study will be described in an informed consent document. This includes information about possible effects and other options of treatment.

Risks associated with the study medicines Participants may have unwanted effects of the medicines used in this study. These unwanted effects can be mild to severe, even life-threatening, and vary from person to person. During this study, participants will have regular check-ups to see if there are any unwanted effects.

Divarasib, sotorasib and adagrasib Participants will be told about the known unwanted effects of divarasib, sotorasib and adagrasib, and possible unwanted effects based on human and laboratory studies or knowledge of similar medicines.

Known unwanted effects of divarasib include throwing up, wanting to throw up, frequent watery stools and irritation in the throat.

Known unwanted effects of sotorasib include stomach pain, back pain, feeling or being sick, fever, difficulty pooping and frequent watery stools.

Known unwanted effects of adagrasib include feeling less hungry than usual, feeling or being sick, frequent watery stools and feeling tired or weak.

Divarasib, sotorasib and adagrasib will be given as a tablet to be swallowed.

The study medicine(s) may be harmful to an unborn baby. Women and men must take precautions to avoid exposing an unborn baby to the study treatment.

Inclusion Criteria:

- Unequivocal histologically or cytologically confirmed diagnosis of metastatic or locally advanced NSCLC not amenable to treatment with surgical resection or combined chemoradiation
- Disease progression during or after treatment with at least one prior systemic therapy but no more than three lines of prior systemic therapy in the advanced or metastatic setting
- Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Documentation of the presence of a KRAS G12C mutation
- Availability of a representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or 10-15 (15 preferred) unstained, freshly cut, serial slides with an associated pathology report
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy of >= 12 weeks

Exclusion Criteria:

- Known hypersensitivity to any of the components of divarasib, or sotorasib or adagrasib

- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Known concomitant second oncogenic driver
- Mixed small-cell lung cancer or large cell neuroendocrine histology
- Known and untreated, or active central nervous system (CNS) metastases
- Leptomeningeal disease or carcinomatous meningitis
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures biweekly or more frequently
- Any infection that, in the opinion of the investigator, could impact patient safety, or treatment with therapeutic oral or IV antibiotics within 14 days prior to Day 1 of Cycle 1
- Prior treatment with any KRAS G12C inhibitor or pan-KRAS/RAS inhibitor
- More than 30 Gy of radiotherapy to the lung within 6 months of randomization
- Uncontrolled tumor-related pain
- Unresolved toxicities from prior anticancer therapy
- History of malignancy within 5 years prior to screening, with the exception of the cancer under investigation in this study and malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%), such as adequately treated carcinoma in situ of the cervix, nonmelanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer