ForPatients
by Roche

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

A study to look at how safe divarasib is when given on its own or in combination with other anti-cancer therapies, and how well these medicines work in people with untreated non-small cell lung cancer that has a KRAS G12C mutation and has spread

A Study Evaluating the Safety, Activity, and Pharmacokinetics of Divarasib in Combination With Other Anti-Cancer Therapies in Participants With Previously Untreated Advanced or Metastatic Non-Small Cell Lung Cancer With a KRAS G12C Mutation

Trial Status	Trial Runs In	Trial Identifier
Recruiting	18 Countries	NCT05789082 2022-003048-28 2023-507171-22-00 BO44426

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 Ib/II, Open-Label, Multicenter Study Evaluating the Safety, Activity, and Pharmacokinetics of Divarasib as a Single Agent or in Combination With Other Anti-Cancer Therapies in Patients With Previously Untreated Advanced Or Metastatic Non-Small Cell Lung Cancer With a KRAS G12C Mutation

Trial Summary:

The purpose of this study is to evaluate the safety, pharmacokinetics (PK), and activity of single-agent divarasib or combined with other anti-cancer therapies in participants with previously untreated, advanced or metastatic non-small cell lung cancer (NSCLC).

Hoffmann-La Roche	Phase 1/Phase 2
Sponsor	Phase

NCT05789082 2022-003048-28 2023-507171-22-00 BO44426
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	#18 Years	No

1. Why is this study needed?

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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. New treatments are needed for people living with NSCLC that has spread to nearby tissue or to other parts of the body.

Standard first treatment for NSCLC that has spread includes a type of medicine that helps the body's natural defence (immune system) attack cancer cells (known as 'immunotherapy'). Immunotherapy, such as pembrolizumab, can be given with or without chemotherapy. Pembrolizumab treatment works better against cancer cells that have a protein called PD-L1 – a protein that works like a brake to keep the immune system from attacking cancer cells.

Around 1 in 10 people with NSCLC have cancer cells with a particular change (mutation) in the KRAS gene called a KRAS G12C mutation. This change makes the cancer cells grow out of control. Research has shown that NSCLC cells with a KRAS G12C mutation often have PD-L1 on them as well.

This study is testing a medicine called divarasib. It is being developed to treat NSCLC that has a KRAS G12C mutation. Divarasib is an experimental medicine. This means health authorities (like the U.S. Food and Drug Administration and the European Medicines Agency) have not approved divarasib on its own or given in combination with anti-cancer therapies for the treatment of NSCLC.

This study aims to test how safe, and how well, divarasib works against NSCLC with the KRAS G12C mutation, when given on its own or with other anti-cancer therapies.

2. Who can take part in the study?

People of at least 18 years of age with NSCLC that has spread and has a KRAS G12C mutation can take part in the study. People may not be able to take part in this study if their NSCLC can be removed with surgery, they have already been treated for NSCLC that has spread or they have been given certain treatments before, including KRAS G12C medicines. People with NSCLC that has spread to the brain or spinal cord cannot take part if it causes symptoms. People with certain other medical conditions, such as heart problems or hepatitis virus infection cannot take part. People who are pregnant, or currently breastfeeding cannot take part in the study.

3. How does this study work?

People will be screened to check if they are able to participate in the study. The screening period will take place from 1 month before the start of treatment. Everyone who joins this study will be placed into 1 of 4 groups (A, B, C or D) depending on when they start the trial, if their NSCLC has PD-L1, and if it has spread to the brain or spinal cord.

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Everyone will be given divarasib as a tablet to be swallowed every day. Groups A and B will also be given pembrolizumab as a drip into a vein (infusion) every 3 weeks. Group B will also be given platinum-based chemotherapy and pemetrexed as an infusion every 3 weeks. After 4 infusions the platinum-based chemotherapy will be stopped. Divarasib will be given with the standard dose of the other anti-cancer therapies.

Some participants in Group A may join 1 of 2 stages of the study, depending on when they join the trial. Small groups of people who join the second stage will be given different doses of divarasib. They will have an equal chance of being placed in any dose group.

Participants in Groups A and B may also be given a medicine to reduce the feeling of nausea (wanting to throw up) during the first 6 weeks of treatment and a medicine that reduces inflammation (a steroid called ‘dexamethasone’) throughout treatment.

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 every week for the first 6 weeks, 4 times over the next 6 weeks, and then 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 1 month after completing the study treatment then visits or telephone calls every 3 months for as long as they agree to it. The study doctor will check on the participant’s wellbeing during follow-up visits or calls. Total time of participation in the study could be more than 5 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 how safe the medicines are, is the number of unwanted effects participants have.

Other key results measured in the study include:

- How many participants have a reduction of their cancer after treatment
- How much time there is between participants’ cancer first responding to treatment and the cancer getting worse
- How long participants live without their cancer getting worse
- How many participants in Group D have a reduction of cancer in the brain after treatment
- How often and how bad unwanted effects are, and how much they affect daily life
- How divarasib gets to different parts of the body, and how the body changes and gets rid of it
- What is the safest, most effective dose of divarasib to use with other anti-cancer therapies

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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 drugs Participants may have unwanted effects of the drugs 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, pembrolizumab and chemotherapy (pemetrexed with carboplatin or cisplatin) Participants will be told about the known unwanted effects of divarasib, pembrolizumab and chemotherapy and possible unwanted effects based on human and laboratory studies or knowledge of similar medicines.

Known unwanted effects of divarasib include frequent watery stools, throwing up or wanting to throw up and higher than usual levels of liver proteins. Known unwanted effects of pembrolizumab include a reaction to the drip into a vein, stomach pain, wanting to throw up, throwing up, feeling tired or weak, and feeling less hungry than usual. Known unwanted effects of chemotherapy include throwing up, wanting to throw up, a low number of red blood cells, frequent watery stools, and hair loss.

Pembrolizumab and chemotherapy will be given as a drip into a vein. Known unwanted effects of a drip into a vein include throwing up, wanting to throw up, a feeling of coldness that makes the body shiver, low or high blood pressure, fever, pain or discomfort in the head, frequent watery stools, shortness of breath, and cough.

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:

- Confirmation of Biomarker eligibility
- Pre-treatment tumor tissue along with an associated pathology report is required for all participants enrolled on study. Representative tumor specimens must be in formalin-fixed, paraffin embedded (FFPE) blocks (preferred) or 15 unstained, freshly cut, serial slides. Although 15 slides are required, if

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only 10 slides are available, the participant may be eligible for the study following consultation with the Sponsor.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
- Histologically or cytologically documented locally advanced unresectable or metastatic NSCLC that is not eligible for curative surgery and/or definitive chemoradiotherapy
- No prior systemic treatment for advanced unresectable or metastatic NSCLC
- Measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additionally, for participants in cohort D, measurable brain metastases defined as at least 5 millimeters and twice the slice thickness, but less than 20 mm, that is asymptomatic and does not require local therapy at the time of enrollment.

Exclusion Criteria:

- Known concomitant second oncogenic driver with available targeted treatment
- Squamous cell histology NSCLC
- Symptomatic, untreated, or actively progressing CNS metastases (Cohorts A, B, and C)
- Prior treatment with a KRAS G12C inhibitor
- Known hypersensitivity to any of the components of divarasib or pembrolizumab; or known hypersensitivity to pemetrexed, carboplatin, or cisplatin (Cohort B only)
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis, active tuberculosis, significant cardiovascular disease within 3 months prior to initiation of study treatment
- History of malignancy other than NSCLC within 5 years prior to initiation of study treatment, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate more >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal breast carcinoma in situ, or Stage I uterine cancer
- Uncontrolled tumor related pain, pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures, uncontrolled or symptomatic hypercalcemia
- Co-morbid condition that is an absolute contraindication to treatment with corticosteroids
- Inability or unwillingness to take prophylactic treatments such as corticosteroids, anti-emetics, folic acid, or vitamin B12 supplementation.
- Participants with brain metastases for whom complete surgical resections is clinically appropriate

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