ForPatients
by Roche

Non Small Cell Lung Carcinoma

A study to compare divarasib plus pembrolizumab with standard treatment (pembrolizumab plus chemotherapy) in people with untreated non-small cell lung cancer that has a change in a gene called KRAS G12C and has spread

A Study Evaluating the Efficacy and Safety of Divarasib and Pembrolizumab Versus Pembrolizumab and Pemetrexed and Carboplatin or Cisplatin in Participants With Previously Untreated, KRAS G12C-Mutated, Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer

Trial Status	Trial Runs In	Trial Identifier
Recruiting	28 Countries	NCT06793215 2024-518365-10-00 CO45042

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 Study Evaluating the Efficacy and Safety of Divarasib and Pembrolizumab Versus Pembrolizumab and Pemetrexed and Carboplatin or Cisplatin in Patients With Previously Untreated, KRAS G12C-Mutated, Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer

Trial Summary:

The purpose of this study is to evaluate the efficacy and safety of divarasib and pembrolizumab compared with pembrolizumab and pemetrexed and carboplatin or cisplatin, for the first-line treatment of adult participants with KRAS G12C-mutated, advanced or metastatic non squamous non-small cell lung cancer (NSCLC).

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Phase 3
Phase

NCT06793215 2024-518365-10-00 CO45042
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers

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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 first treatment for NSCLC that has spread includes a type of medicine that helps a person's natural defence (immune system) to attack cancer cells, called 'immunotherapy'. Immunotherapy, such as pembrolizumab, is usually given with platinum-based chemotherapy. Around 1 in 10 people with NSCLC have a specific change (mutation) in their *KRAS* gene called a *KRAS G12C* mutation. This causes cancer cells to grow out of control. Combining immunotherapy with therapy that targets this mutation may work better than current standard treatment for NSCLC with this type of mutation.

This study is testing a combination of medicines called divarasib plus pembrolizumab. It is being developed to treat previously untreated NSCLC that has spread. Divarasib is a targeted therapy that may work well against NSCLC with a *KRAS G12C* mutation. Divarasib is an experimental medicine. This means health authorities (like the U.S. Food and Drug Administration and European Medicines Agency) have not approved divarasib on its own or in combination with pembrolizumab for the treatment of NSCLC. This study aims to compare the effects of divarasib plus pembrolizumab versus standard first treatment (pembrolizumab plus chemotherapy) in people with NSCLC with a *KRAS G12C* mutation that has spread.

2. Who can take part in the study?

People of at least 18 years of age who have not been treated previously for NSCLC that has spread can take part in the study if they cannot be treated with surgery, chemotherapy or radiotherapy with an intent to cure. The NSCLC must also have a change known as 'G12C' in the *KRAS* gene. People may not be able to take part if they have a type of NSCLC that starts in flat cells known as squamous cells, if NSCLC has spread to the brain or spinal cord and causes symptoms, or if the NSCLC has other changes in certain genes and there are specific treatments available for it. 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 2 groups randomly (like flipping a coin) and given either:

- Divarasib, given as a tablet (to be swallowed) every day plus pembrolizumab, given as a drip into the vein every 3 weeks OR

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- Pembrolizumab plus platinum-based chemotherapy, given as drips into the vein every 3 weeks

Participants will have an equal chance of being placed in either group. 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 1 to 3 weeks. They will see how well the treatment is working and any unwanted effects participants may have. Participants will receive treatment until their disease worsens or unwanted effects are not tolerable. Participants will have a follow-up visit 1 month after completing the study treatment, during which the study doctor will check on the participant's wellbeing. The study doctor will continue to check on participants' health by visits, telephone calls, or through their medical records every 3 months for as long as they agree to it, until the study ends. Total time of participation in the study could be more than 5 years depending when a person joins. 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 results measured in the study assess if the medicine has worked by looking at how long participants live and how long participants live without their cancer getting worse.

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 the participant's cancer first responding to treatment and the cancer getting worse
- Change in participants' health and how their cancer symptoms impact their daily life and their ability to function and enjoy life
- The number of participants with scores that improve, worsen, or stay the same in questionnaires which measure how well they can function and how their lung cancer affects their daily life
- The time it takes for a person to have a significant worsening in cancer symptoms (cough, difficulty breathing and chest pain) and their ability to function and enjoy life
- The number and seriousness of unwanted effects

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.

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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 divarasib, pembrolizumab and chemotherapy (pemetrexed, carboplatin and cisplatin) 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. 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 these medicines include frequent watery stools and throwing up. Known unwanted effects of a drip into a vein include throwing up, low or high blood pressure, fever, pain or discomfort in the head, frequent watery stools, shortness of breath, cough, and hair loss.

The study medicines 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:

- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Histologically or cytologically confirmed diagnosis of advanced or metastatic non squamous NSCLC that is not eligible for curative surgery and/or definitive chemoradiotherapy
- Measurable disease, as defined by RECIST v1.1
- No prior systemic treatment for advanced or metastatic NSCLC
- Documentation of the presence of a KRAS G12C mutation
- Documentation of known PD-L1 expression status in tumor tissue
- Availability of a representative tumor specimen
- Adequate end-organ function
- Eligible to receive a platinum-based chemotherapy regimen

Exclusion Criteria:

Exclusion Criteria Related to NSCLC:

- Known concomitant second oncogenic driver with available targeted treatment
- Symptomatic, untreated, or actively progressing central nervous system (CNS) metastases
- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for >=2 weeks prior to randomization
- History of leptomeningeal disease
- Uncontrolled tumor-related pain

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- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)

Exclusion Criteria Related to Current or Prior Treatments:

- Any anti-cancer systemic therapy, including hormonal therapy, within 21 days prior to randomization, or is expected to require any other form of antineoplastic therapy while in the study
- Radiation therapy including palliative RT to bone metastases within 2 weeks prior to randomization and RT to the lung >30Gy within 6 months prior to randomization
- Prior treatment with KRAS G12C inhibitors or pan-KRAS/RAS inhibitors
- Treatment with systemic immunosuppressive or immunostimulatory medications, including CD137 agonists and immune checkpoint inhibitors
- Current treatment with medications that are well known to prolong the QT interval
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to randomization
- Prior allogeneic stem cell or solid organ transplantation

Exclusion Criteria Related to General Health:

- History of malignancy other than NSCLC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year overall survival [OS] rate >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
- Individuals with chronic diarrhea, short bowel syndrome or significant upper gastrointestinal surgery including gastric resection, a history of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or any active bowel inflammation (including diverticulitis), malabsorption syndrome, conditions that would interfere with enteral absorption
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on the screening chest computed tomography scan
- Significant cardiovascular disease within 3 months prior to screening

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