ForPatients
by Roche

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

A clinical trial to look at how alectinib and entrectinib each work to reduce certain signs of cancer compared with durvalumab in people with advanced non-small cell lung cancer with specific abnormal genes, and how safe alectinib and entrectinib are

A Study Evaluating the Efficacy and Safety of Multiple Therapies in Cohorts of Participants With Locally Advanced, Unresectable, Stage III Non-Small Cell Lung Cancer (NSCLC)

Trial Status	Trial Runs In	Trial Identifier
Recruiting	30 Countries	NCT05170204 2023-503920-14-00 BO42777

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 I–III, multicenter study evaluating the efficacy and safety of multiple therapies in cohorts of patients selected according to biomarker status, with locally advanced, unresectable, stage III non-small cell lung cancer

Trial Summary:

This study will evaluate the efficacy and safety of multiple therapies in participants with locally advanced, unresectable, Stage III NSCLC with eligible biomarker status as determined by Version 8 of the American Joint Committee on Cancer/Union for International Cancer Control NSCLC staging system.

Hoffmann-La Roche	Phase 3
Sponsor	Phase

NCT05170204 2023-503920-14-00 BO42777
Trial Identifiers

Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	#18 Years	No

1. Why is the BO42777 clinical trial needed?

Non-small cell lung cancer (NSCLC) that has not spread in the body and cannot be removed by surgery is known as ‘locally advanced unresectable NSCLC’. The current standard treatment is chemoradiotherapy. This may be followed by treatment with a drug called durvalumab, depending on which country you live in. Sometimes NSCLC continues to get worse after standard treatment, so new treatments are needed.

Alectinib and entrectinib are treatments that can stop cancer from growing and spreading to other parts of the body. Alectinib and entrectinib target cancer cells that have certain changes (called mutations) in the *ALK* or *ROS1* genes. They have not yet been approved to treat locally advanced unresectable NSCLC.

This clinical trial aims to compare the effects, good or bad, of alectinib and entrectinib against durvalumab in people with locally advanced unresectable NSCLC with *ALK* or *ROS1* gene mutations.

2. How does the BO42777 clinical trial work?

This clinical trial is recruiting people with locally advanced unresectable NSCLC that has *ALK* or *ROS1* gene mutations. People can take part if they have been treated with at least two cycles of chemoradiotherapy within 6 weeks before starting the trial and their cancer has not gotten worse during or following chemoradiotherapy.

People who take part in this clinical trial (participants) will be given the clinical trial treatment alectinib or entrectinib for up to 3 years OR durvalumab for up to 1 year. The clinical trial doctor will see them every 2 weeks for the first 3 months, then once a month while being given treatment. These hospital visits will include checks to see how the participant responds to the treatment and any side effects they may have. Some visits may be conducted at the participant’s home or local clinic (depending on the clinical trial doctor’s instructions and different country’s requirements). After the last dose of treatment, participants will be followed-up every 1 to 3 months at clinic visits, by telephone or through their medical records, for as long as they agree to it. The total time of participation in the clinical trial will depend on how the cancer is controlled by the trial treatment and could be more than 8 years. Participants can stop trial treatment and leave the clinical trial at any time.

3. What are the main endpoints of the BO42777 clinical trial?

The main clinical trial endpoint (the main result measured in the trial to see if the drug has worked) is the amount of time between the start of the trial and participants’ cancer worsening.

The other clinical trial endpoints include:

- The amount of time between the start of the trial and cancer spreading in the brain or body
- The number of participants whose tumours have got smaller and the amount of time this lasts if disease then progresses
- How long participants live
- The amount of time between the start of the trial and participants' quality of life or cancer symptoms (cough, chest pain or shortness of breath) getting worse
- The number of participants with no worsening of, or improved, quality of life and cancer symptoms
- The number and seriousness of side effects

4. Who can take part in this clinical trial?

People can take part in this trial if they are at least 18 years old and are willing and able to use the device or apps provided for questionnaires.

People cannot take part in this trial if they have NSCLC that has spread in the body or that has certain other gene mutations. People may also not be able to take part in this trial if they have certain other medical conditions, such as heart conditions, liver disease or certain infections, have had or are receiving certain treatments, have ongoing side effects from previous cancer treatments, are involved in another clinical trial or are unable to swallow pills. People who are pregnant, breastfeeding or planning to become pregnant during or soon after the clinical trial also cannot take part.

5. What treatment will participants be given in this clinical trial?

Everyone who joins this clinical trial will be placed into a treatment group depending on which mutation is present in their lung cancer (*ALK* or *ROS1*), and will be given either:

Group A1 (participants with ALK-positive NSCLC)

- Alectinib given as oral pills twice daily with food for up to 3 years
- OR durvalumab given as infusions into the vein every 4 weeks for up to 1 year

Group A2 (participants with ROS1-positive NSCLC)

Note: Group A2 is now closed – no new participants will join this group.

- Entrectinib given as oral pills once daily with or without food for up to 3 years
- OR durvalumab given as infusions into the vein every 4 weeks for up to 1 year

Participants in each group (A1 or A2) will have an equal chance of receiving one of the targeted therapies or durvalumab. People in certain countries may be unable to join a specific treatment group due to the restrictions of the country they live in.

This is an open-label trial, which means everyone involved, including the participant and the clinical trial doctor, will know the clinical trial treatment the participant has been given.

6. Are there any risks or benefits in taking part in this clinical trial?

The safety or effectiveness of the experimental treatment or use may not be fully known at the time of the trial. Most trials involve some risks to the participant. However, it may not be greater than the risks related to routine medical care or the natural progression of the health condition. People who would like to participate will be told about any risks and benefits of taking part in the clinical trial, as well as any additional procedures, tests or assessments they will be asked to undergo. All of these will be described in an informed consent document (a document that provides people with the information they need to decide to volunteer for the clinical trial).

Risks associated with the clinical trial drugs

Participants may have side effects (an unwanted effect of a drug or medical treatment) from the drugs used in this clinical trial. Side effects can be mild to severe, even life-threatening, and vary from person to person. Participants will be closely monitored during the clinical trial; safety assessments will be performed regularly.

Alectinib, entrectinib and durvalumab

Participants will be told about the known side effects of alectinib, entrectinib or durvalumab and possible side effects based on human and laboratory studies or knowledge of similar drugs. Alectinib or entrectinib will be given as a pill to be swallowed, and durvalumab will be given as an infusion into the vein (intravenous infusion). Participants will be told about any known side effects of swallowing pills or intravenous infusions.

Potential benefits associated with the clinical trial

Participants' health may or may not improve from participation in the clinical trial. Still, the information collected may help other people with similar medical conditions in the future.

Inclusion Criteria:

Inclusion Criteria (All Cohorts):

- Body weight >/= 30 kg at screening
- Willingness and ability to use the electronic device(s) or application(s) for the electronic patient-reported outcome (PRO)
- Whole-body positron emission tomography/computed tomography scan (PET/CT) (from the base of skull to mid-thighs) for the purposes of staging, performed prior and within 42 days of the first dose of cCRT or sCRT

- Histologically or cytologically documented locally advanced, unresectable Stage III NSCLC of either squamous or non-squamous histology
- Prior receipt of at least two prior cycles of platinum-based chemotherapy given concurrently with radiotherapy (cCRT); or at least two prior cycles of platinum-based chemotherapy given prior to radiotherapy (sCRT)
- The RT component in the cCRT or sCRT must have been at a total dose of radiation of 60 (+/-10%) Gy (54 Gy to 66 Gy) administered by intensity-modulated radiotherapy (preferred) or three dimension (3D)-conforming technique
- No disease progression during or following platinum-based cCRT or sCRT
- Life expectancy >/= 12 weeks
- Confirmed availability of a representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen
- Documented tumor PD-L1 status (TC score < 1% vs. >/= 1% vs. unknown) as determined: centrally with the SP263 IHC assay on the confirmed available FFPE tumor specimen; locally, with the SP263 (preferred) or 22C3 IHC assays
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- Adequate hematologic and end-organ function
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined by the protocol
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined by the protocol

Inclusion criteria specific to Cohort A1:

- Documented ALK fusion positivity by an eligible result from: centralized multiplex molecular testing of tumor tissue at the Sponsor's designated central laboratory under Study BX43361 or available results from a Sponsor pre-approved local, appropriately validated ALK fusion test on tumor tissue performed in a Clinical Laboratory Improvement Amendments certified or equivalent laboratory

Inclusion criteria specific to Cohort A2:

- Documented ROS1 fusion positivity by an eligible result from: centralized multiplex molecular testing of tumor tissue at the Sponsor's designated central laboratory under Study BX43361 or available results from a Sponsor pre-approved local, appropriately validated ROS1 fusion test on tumor tissue performed in a Clinical Laboratory Improvement Amendments certified or equivalent laboratory
- Ability to swallow entrectinib intact, without chewing, crushing, or opening the capsules

Exclusion Criteria:

Exclusion Criteria (All Cohorts):

- Any history of previous NSCLC and/or any history of prior treatment for NSCLC (patients must be newly diagnosed with unresectable Stage III disease)
- Any evidence of Stage IV disease, including, but not limited to, the following: pleural effusion, pericardial effusion, brain metastases, history of intracranial hemorrhage or spinal cord hemorrhage, bone metastases, distant metastases
- If a pleural effusion is present, the following criteria must be met to exclude malignant involvement (T4 disease): when pleural fluid is visible on both the CT scan and chest X-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative; participants with exudative pleural effusions are excluded regardless of cytology; participants with effusions that are minimal (i.e., not visible on chest X-ray) that are too small to safely tap are eligible

- NSCLC known to have a known or likely oncogenic-driver mutation in the EGFR gene, as identified by site local testing or Sponsor central testing
- Liver disease, characterized by any of the following: impaired excretory function (e.g., hyperbilirubinemia), synthetic function, or other conditions of decompensated liver disease, such as coagulopathy, hepatic encephalopathy, hypoalbuminemia, ascites, and bleeding from esophageal varices or active viral or active autoimmune, alcoholic, or other types of acute hepatitis
- Positive hepatitis B surface antigen (HBsAg) test at screening
- Participants known to be positive for hepatitis C virus (HCV) antibody (Ab) are excluded with the following exception: participants who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution are eligible
- HIV infection: participants are excluded if not well-controlled as defined by the protocol
- Known active tuberculosis
- 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 CT scan
- Grade >/= 2 pneumonitis from prior cCRT or sCRT
- Any Grade > 2 unresolved toxicity from prior cCRT or sCRT
- Any gastrointestinal (GI) disorder that may affect absorption of oral medications, such as malabsorption syndrome or status post-major bowel resection
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions: participants with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study; participants with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study
- 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 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
- Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer
- Major surgical procedure, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the final dose of study treatment
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor-alpha agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with exceptions defined by the protocol
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-cytotoxic T lymphocyte-associated protein 4, anti-TIGIT, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Prior allogeneic stem cell or solid organ transplantation
- Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study

- Any condition that, in the opinion of the investigator, would interfere with the evaluation of the study drug or interpretation of patient safety or study results
- Any prior Grade >/= 3 immune-mediated adverse event or any unresolved Grade > 1 immune-mediated adverse event while receiving any previous immunotherapy agent other than immune checkpoint blockade agents

Exclusion criteria specific to Cohort A1:

- Presence of clinically symptomatic interstitial lung disease or interstitial pneumonitis, including radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention)
- NSCLC known to have one or more of the following ALK point mutations, as identified by site local testing or Sponsor central testing: I1171X (where X is any other amino acid), V1180L, G1202R
- Symptomatic bradycardia
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina; participants with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
- Prior treatment with ALK inhibitors
- History of hypersensitivity to alectinib, durvalumab, or any of their excipients
- Inability to swallow oral study drug
- Known hereditary problems of galactose intolerance, a congenital lactase deficiency, or glucose-galactose malabsorption
- Pregnancy or breastfeeding, or intending to become pregnant during the study treatment or within 90 days after the final dose of alectinib or durvalumab

Exclusion criteria specific to Cohort A2:

- Symptomatic bradycardia
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina; participants with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
- Left ventricular ejection fraction less than or equal to 50% observed during the screening for the study
- History of prolonged QTc interval (e.g., repeated demonstration of a QTc interval > 450 ms from ECGs performed at least 24 hours apart)
- History of additional risk factors for torsade de pointes (e.g., family history of long QT syndrome)
- Familial or personal history of congenital bone disorders or bone metabolism alterations
- Incomplete recovery from any surgery prior to the start of study treatment that would interfere with the determination of safety or efficacy of the treatment
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
- Prior treatment with ROS1 inhibitors
- History of hypersensitivity to entrectinib, durvalumab, and their excipients
- Grade >/= 3 toxicities due to any prior therapy (e.g., RT) (excluding alopecia) that have not shown improvement or are not stable and are considered to interfere with current study drug

- Known hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
- Grade >/= 2 peripheral neuropathy
- Pregnancy or intention of becoming pregnant during study treatment, within 35 days after the final dose of entrectinib, or within 90 days after the final dose of durvalumab