A Phase 3, randomized, open label study of lorlatinib (PF 06463922) monotherapy versus crizotinib monotherapy in the first line treatment of patients with advanced ALK positive non small cell lung cancer

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This study has been transitioned to CTIS with ID 2023-509169-19-00 check the CTIS register for the current data. To demonstrate that lorlatinib as a single agent (Arm A) is superior to crizotinib alone (Arm B) in prolonging Progression-Free Survival...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON54681

Source
ToetsingOnline

Brief title
B7461006 - ALK positive non small cell lung cancer

Condition

- Other condition
- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
Non small cell lung cancer

Health condition

advanced ALK positive non small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: industry

Intervention

Keyword: advanced ALK positive non small cell lung cancer, lorlatinib, open label

Outcome measures

Primary outcome

PFS based on blinded independent central review (BICR) assessment (RECIST v.1.1).

Secondary outcome

Efficacy: OS, PFS based on Investigator*s assessment, OR based on BICR and on Investigator*s assessment; intracranial OR (IC-OR),IC-TTP, DR and IC-DR, TTR and ICTTR all by BICR (RECIST v. 1.1) and PFS2;ICOR, IC-TTP, IC-DR, IC-TTR and DR based on the investigator's assessment.

Safety: AEs (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate) and body weight; electrocardiograms (ECGs); echocardiogram or MUGA scan; ophthalmologic data;

PROs as assessed by EORTC QLC-C30, EORTC QLQ-LC13, EQ-5D-5L;

Tumor tissue biomarkers including, but not limited to, ALK gene rearrangement and/or mutation as measured by next-generation sequencing (NGS) and/or immunohistochemistry (IHC);

Peripheral blood cfDNA (circulating free Deoxyribonucleic acid) biomarkers including, but not limited to, ALK gene rearrangement and/or ALK kinase domain mutations.

Study description

Background summary

Non-small cell lung cancer (NSCLC) is the most common cause of fatal malignancy globally, most often diagnosed in advanced stages, where surgery and local radiotherapy are no longer curative or indicated.Standard therapy in advanced stages of disease is primarily palliative in nature, involving the use of cytotoxic chemotherapy with or without radiation therapy or immunotherapy. Targeted therapies such as tyrosine kinase inhibitors (TKIs) may be used for appropriate patients. In spite of these treatments, 5-year survival is only about 17% for advanced stage NSCLC patients, highlighting the need for novel therapies and treatment regimens.

Study objective

This study has been transitioned to CTIS with ID 2023-509169-19-00 check the CTIS register for the current data.

To demonstrate that lorlatinib as a single agent (Arm A) is superior to crizotinib alone (Arm B) in prolonging Progression-Free Survival (PFS) in advanced ALK-positive NSCLC participants who are treatment naive.

Study design

This is a Phase 3, multinational, multicenter, randomized, open-label, parallel 2-arm study in which approximately 280 previously untreated patients with advanced ALK-positive NSCLC will be randomized 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy.

Intervention

Arm A: Lorlatinib monotherapy at the recommended Phase 2 dose (RP2D) of 100 mg QD, administered as 4 x 25 mg oral tablets, continuously; or

Arm B: Crizotinib monotherapy at the registered starting dose of 250 mg BID, administered as 1 x 250 mg oral capsules, twice daily, continuously.

Each cycle duration will be 28 days.

Study burden and risks

During the study the patient has to come to the clinic until disease progression. During these visits a physical examination is done and blood will be taken. In addition the subject needs to complete some questionnaires.

Potential side effects are listed in the Investigators Brochure and are summarized in the patient information sheet.
The Benefit/Risk assessment is explained in the protocol section: 1.2.8.

The Sponsor plans to closely monitor the safety profile for new emerging safety risks or increased frequency or severity of anticipated risks based on a review of aggregate data.

Contacts

Public
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Scientific
Pfizer

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

see section 4.1 in protocol:
1.Diagnosis:
a.Study Population: Patients with histologically or cytologically confirmed diagnosis of locally advanced [(Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) by American Joint Committee on Cancer (AJCC) v 7.0] ALK-positive NSCLC where ALK status is determined by the FDA-approved (for use in US), CE (Conformité Européene) marked (for EU and other countries that accept CE marking), and PMDA(Pharmaceuticals and Medical Devices Agency)- approved (for use in Japan) Ventana ALK (D5F3) Companion Diagnostic (CDx) IHC test performed on the Ventana ULTRA or XT platforms (refer to Section 6.1.1.1 for any prescreening activity related to ALK determination);
b. Tumor Requirements: At least 1 extracranial measurable target lesion per RECIST v. 1.1 that has not been previously irradiated. CNS metastases are allowed if:
i.Asymptomatic: either not currently requiring corticosteroid treatment, or on a stable or decreasing dose of <= 10 mg QD prednisone or equivalent; or
ii. Previously diagnosed and treatment has been completed with full recovery from the acute effects of radiation therapy or surgery prior to randomization, and if corticosteroid treatment for these metastases has been withdrawn for at least 4 weeks with neurological stability; or
iii. Leptomeningeal disease (LMD) or carcinomatous meningitis (CM) if visualized on MRI (magnetic resonance imaging), or if baseline CSF positive cytology is available.
c. Tissue Requirements: All participants must have an archival formalin fixed, paraffin embedded (FFPE) tissue specimen available and collected prior to randomization. If archived tissue is unavailable, then a mandatory de novo biopsy must be performed.
2. No prior systemic NSCLC treatment,, including molecularly targeted agents, angiogenesis inhibitors, immunotherapy, or chemotherapy. Adjuvant/neoadjuvant NSCLC treatment only allowed if completed more than 12 months prior to randomization.
3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, 1, or 2.
4. Age >=18 years (or >=20 years as required by local regulation).

5. Adequate Bone Marrow Function, including:
a. Absolute Neutrophil Count (ANC) >= 1,500/mm3 or >= 1.5 x 109/L;
b. Platelets >=100,000/mm3 or >=100 x 109/L;
c. Hemoglobin >= 9 g/dL.
6. Adequate Pancreatic Function, including:
a. Serum total amylase <= 1.5 x upper limit of normal (ULN)*;
b. Serum lipase <= 1.5 x ULN.
*if total amylase > 1.5 x ULN, but pancreatic amylase is within the ULN, then patient may be enrolled
7. Adequate Renal Function, including:
a. Serum creatinine <= 1.5 x ULN or estimated creatinine clearance >= 60 mL/min as calculated using the method standard for the institution.
8. Adequate Liver Function, including:
a. Total serum bilirubin <= 1.5 x ULN;
b. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) <= 2.5 x ULN (<= 5.0 x ULN in case of liver metastases);
9. Acute effects of prior radiotherapy resolved to baseline severity or to CTCAE Grade <=1 except for AEs that in the investigator*s judgment do not constitute a safety risk for the participant.
10. Serum pregnancy test (for females of childbearing potential) negative at screening. Female participants of non-childbearing potential must meet at least 1 of the following criteria:
• Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
• Have undergone a documented hysterectomy and/or bilateral oophorectomy;
• Have medically confirmed ovarian failure.
All other female participants (including female participants with tubal ligations) are considered to be of childbearing potential.
11. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
12. Willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

Exclusion criteria

See protocol section 4.2:
Patients with any of the following characteristics/conditions will not be included in the study:
1. Spinal cord compression unless the participant has good pain control attained through therapy, and there is stabilization or recovery of neurological function for the 4 weeks prior to randomization.
2. Major surgery within 4 weeks prior to randomization. Minor surgical

procedures (eg, port insertion) are not excluded, but sufficient time should have passed for adequate wound healing.
3. Radiation therapy within 2 weeks prior to randomization, including stereotactic or partial brain irradiation. Patients who complete whole brain irradiation within 4 weeks prior to randomization or palliative radiation therapy outside of the CNS within 48 hours prior to randomization will also not be included in the study.
4. Gastrointestinal abnormalities, including inability to take oral medication; requirement for intravenous alimentation; prior surgical procedures affecting absorption including total gastric resection or lap band; active inflammatory gastrointestinal disease, chronic diarrhea, symptomatic diverticular disease; treatment for active peptic ulcer disease in the past 6 months; malabsorption syndromes.
5. Known prior or suspected severe hypersensitivity to study drugs or any component in their formulations.
6. Active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV) or hepatitis C virus (HCV) (e.g., in case of known HBsAg or HCV antibody positivity), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.
7. Clinically significant vascular (both arterial and venous) and nonvascular cardiac conditions, (active or within 3 months prior to enrollment), which may include, but are not limited to:
- Arterial disease such as cerebral vascular accident/stroke (including Transient Ischemic Attack -TIA), myocardial infarction, unstable angina;
- Venous diseases such as cerebral venous thrombosis, symptomatic pulmonary embolism;
-Non-vascular cardiac disease such as congestive heart failure (New York Heart Association Classification Class >= II), second-degree or third-degree AV block (unless paced) or any AV block with PR >220 msec; or ongoing cardiac dysrhythmias of NCI CTCAE Grade >=2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm (unless participant is otherwise healthy such as long-distance runners, etc.), machine-read Electrocardiogram (ECG) with QTc >470 msec, or
congenital long QT syndrome.
8. Patients with predisposing characteristics for acute pancreatitis according to investigator judgment (eg, uncontrolled hyperglycemia, current gallstone disease) in the last month prior to randomization.
9. History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis.
10. Evidence of active malignancy (other than NSCLC, non melanoma skin cancer, in situ cervical cancer, papillary thyroid cancer, lobular carcinoma in situ/ductal carcinoma in situ (LCIS/DCIS) of the breast, or localized prostate cancer) within the last 3 years prior to randomization.
11. Concurrent use of any of the following food or drugs (consult the sponsor if in doubt whether a food or a drug falls into any of the above categories)

within 12 days prior to the first dose of lorlatinib or crizotinib.
a. known strong CYP3A inhibitors (eg, strong CYP3A inhibitors: grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos], boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, ritonavir alone and with danoprevir or
elvitegravir or indinavir or lopinavir or paritaprevir or ombitasvir or dasabuvir or saquinavir or tipranavir, telaprevir, troleandomycin, and voriconazole. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.
b. known CYP3A substrates with narrow therapeutic index, such as astemizole*, terfenadine*, cisapride*, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil, fentanyl (including transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine) (*withdrawn from US market).
c. known strong CYP3A inducers (eg, avasimibe, carbamazepine, phenobarbital, phenytoin, rifatutin, rifampin, St. John*s Wort).
d. known P gp substrates with a narrow therapeutic index (eg, digoxin).
12. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
13. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.
14. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation.
15. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use a highly effective methods of contraception as outlined in this protocol for the duration of the study and for at least 97 days, if male or 35 days if female, after the last dose of investigational product if under lorlatinib or 90 days if under crizotinib.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-10-2017
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	lorlatinib
Product type:	Medicine
Brand name:	xalkori
Generic name:	crizotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-05-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-01-2018

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-04-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	20-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-10-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-03-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-509169-19-00
EudraCT	EUCTR2016-003315-35-NL
ClinicalTrials.gov	NCT03052608
CCMO	NL59791.056.17