Brigatinib in Patients With Anaplastic Lymphoma Kinase-Positive (ALK+), Advanced Non-Small-Cell Lung Cancer (NSCLC) Progressed on Alectinib or Ceritinib

Published: 01-10-2018
Last updated: 30-01-2025

Primary Objectives:To determine the efficacy of brigatinib, as evidenced by confirmed objective response rate (ORR), in patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with alectinib or ceritinib....

Ethical review	Approved WMO
Status	Completed
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON49812

Source
ToetsingOnline

Brief title
Takeda 2002

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer; non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: ARIAD Pharmaceuticals, Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
Source(s) of monetary or material Support: ARIAD Pharmaceuticals;Inc. a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Intervention

Keyword: Advanced Non-Small-Cell Lung Cancer (NSCLC), Anaplastic Lymphoma Kinase-Positive (ALK+), Brigatinib

Outcome measures

Primary outcome

The primary endpoint is confirmed ORR, as assessed by the IRC, per Response

Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the full analysis

set population.

Secondary outcome

Secondary endpoints:

1. Confirmed ORR, as assessed by the investigator, per RECIST version 1.1.

2. DOR as assessed by the investigator and IRC.

3. PFS as assessed by the investigator and IRC.

4. Disease control rate (DCR), defined as best overall response of complete

response (CR), partial response (PR) or stable disease (SD) >=6 weeks by RECIST

version 1.1, as assessed by the investigator and IRC.

5. Time to response as assessed by the investigator and IRC.

6. Confirmed iORR in patients with brain metastases at baseline, as assessed by

the IRC.

7. Duration of intracranial response in patients with brain metastases at

baseline, as assessed by the IRC.

8. Intracranial progression-free survival (iPFS) in patients with brain metastases at baseline, as assessed by the IRC.

9. OS.

Note: The efficacy endpoints will be analyzed in all treated populations and in a subgroup of patients who progressed on prior alectinib. Additional details about subgroup analyses will be provided in the statistical analysis plan (SAP).

10. Safety/tolerability (NCI CTCAE version 4.03).

11. HRQOL assessed with the global health status/quality of life (QOL) and other function and symptom from EORTC QLQ-C30 (version 3.0), and EORTC QLQ-LC13.

Study description

Background summary

General Information:
This study has been designed by Takeda and is being carried out by doctors at various hospitals. Takeda is paying for the costs of this study.
For this study 103 patients from different countries are required.

Background of the study and study drug:
Brigatinib is approved by the U.S. Food and Drug Administration (*FDA*), the regulatory authority in the United States as a treatment for ALK positive metastatic NSCLC patients (i.e. lung cancer that expresses the ALK abnormal gene or protein that has spread within the body) who have received prior treatment with the drug crizotinib. This medicine is not yet approved in your country. In this study, both you and your doctors and nurses in the study hospital know what drug you are taking (this is called "open label").

Study objective

Primary Objectives:
To determine the efficacy of brigatinib, as evidenced by confirmed objective response rate (ORR), in patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with alectinib or ceritinib.

Secondary Objectives:
1. To characterize the durability of efficacy with brigatinib.
2. To assess intracranial efficacy of brigatinib.
3. To assess the overall survival (OS).
4. To assess the safety and tolerability of brigatinib.
5. To collect plasma concentration-time data for brigatinib to contribute to population pharmacokinetic analyses.
6. To assess patient-reported symptoms and health-related quality of life (HRQOL).

Study design

Patients will continue to be treated with brigatinib until they experience objective disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, as assessed by the investigator, or intolerable toxicity. Upon radiological progression, at the discretion of the investigator, patients who were receiving brigatinib at a dose of 180 mg and have not experienced toxicity greater than Grade 2 during the treatment may elect to receive brigatinib at an increased dose of 240 mg QD, or continue study treatment at the current dose in case they are still benefiting from the treatment at this dose. In both scenarios, sponsor medical monitor will review and approve the case.

Intervention

Brigatinib 180 mg QD with a 7-day lead-in at 90 mg QD.
Patients who progressed on brigatinib 180 mg QD dose, did not experience toxicity Grade >2, and signed a separate informed consent will be given the option to receive brigatinib at an increased dose of 240 mg QD.

Study burden and risks

Possible side effects and discomforts

Very common (reported in 10% and more of patients) included:
• Pneumonia or infection that occurs in the lung; symptoms may include cough, shortness of breath, fevers, chills, chest pain, headache, sweating, and weakness
• Low levels of red blood cell count (which can cause you to feel tired)
• Low levels of white blood cell counts (including white blood cell counts overall, as well as certain types of white blood cells: lymphocytes and neutrophils), which could increase the risk of infection
• Activated partial thromboplastin time (APTT) increased (mean a lack of or low level of one of the blood clotting factors or another substance needed to clot blood)
• High blood sugar levels

• High insulin levels which may cause low blood sugar, weakness, mental status changes, and/or weight gain
• Decreased appetite
• Low levels of sodium in the blood
• Low levels of potassium in the blood
• Low levels of magnesium in the blood
• Low levels of phosphate in the blood
• High levels of calcium in the blood
• Headache
• Peripheral neuropathy, a condition in which nerves outside the brain and spinal cord (peripheral nerves) have been damaged which can result in symptoms such as numbness, tingling, prickling sensation, weakness or pain
• Dizziness
• Visual Disturbance
• High Blood Pressure
• Cough
• Shortness of breath
• Nausea
• Diarrhoea
• Vomiting
• Constipation
• Abdominal pain
• Stomatitis (inflammation of the lining of any of the structures in the mouth, including cheeks, gums, tongue, lips, throat and roof or floor of the mouth)
• Increased liver enzymes (Aspartate aminotransferase (AST) increased or Alanine aminotransferase (ALT) increased) which can suggest damage to the liver
• Increased lipase level (an enzyme measured in the blood that reflects function of the pancreas; elevations in lipase may indicate inflammation of the pancreas)
• Increased amylase level (an enzyme measured in the blood that reflects function of the pancreas; elevations in amylase may indicate inflammation of the pancreas)
• Increased alkaline phosphatase level, an enzyme in the blood produced by the liver and other organs
• Skin rash
• Itchy skin
• Increased creatine phosphokinase level (an enzyme measured in the blood, elevations may indicate injury or stress to muscle tissue, the heart, or the brain)
• Muscle pain (including muscle spasms)
• Joint Pain
• Increased creatinine level, which may indicate kidney damage
• Fatigue or tiredness
• Oedema (built up of fluid in the body which causes the affected tissue to become swollen)
• Fever

Common (reported in 1-9% of patients) included:
• Infection involving the upper respiratory tract; symptoms may include congestion, sneezing, coughing, fever, and sore throat
• Low platelets or decreased number of blood cells that help to clot blood. This can be associated with an increased risk of bleeding
• Insomnia or inability to obtain an adequate amount or quality of sleep
• Problems with memory
• Distortion of the sense of taste
• Increased heart rate
• Electrocardiogram QT prolonged (a change in ECG, a study of the electrical system of the heart that may indicate an increased risk of serious abnormalities in the heart*s rhythm)
• Slow heart rate
• Noticeably rapid, strong, or irregular heartbeats
• Pneumonitis (inflammation of the lung) or interstitial lung disease (ILD), diseases that affect the lungs
• Dry Mouth
• Indigestion or upset stomach
• Flatulence or accumulation of gas, usually in excess, that is present in the intestinal tract and passed out of the body from the rectum
• Increased lactate dehydrogenase (LDH) level, an enzyme present in many body tissues, especially the heart, liver, kidney, muscles, brain, blood cells, and lungs. LDH is most often measured to check for tissue damage
• Dry skin
• Increased skin sensitivity to sunlight or lamps
• Musculoskeletal chest pain
• Pain in extremity
• Non*cardiac chest pain
• Pain
• Chest discomfort or pain
• Loss of weight
• High Level of blood cholesterol

Uncommon (reported in less than 1 % of patients) included:
• Muscle and/or bone stiffness

Below you can find more information on the assessments that will be performed during the course of the research study:

• Informed Consent: Before any study procedures can start, you will need to read, confirm understanding, and sign this informed consent if you would like to participate in this study.
• Medical History: A complete medical history, any medications you have used or are currently using, and any cancer therapies you have had in the past. Please note that if you do not provide all the information about your medical history, medicines or supplements you are taking to the study doctor, participating in this study may harm you. It is important for you to share all information with

your study doctor about how you are feeling and any medicines or supplements you are taking.
• Physical Exam & Vital Signs: Your blood pressure, heart rate, height, and weight will be measured. Temperature and breathing rate will also be measured, if needed. Physical exams will be performed by your study doctor throughout the study. Some of these exams will be complete physical exams, while others will be based on the symptoms you are having.
• Eastern Cooperative Oncology Group (ECOG) Status Assessments: Your study doctor will ask you questions and make health assessments about how your cancer is affecting your daily life.
• Questionnaires: You will be asked to answer some questions on paper about how you are feeling and symptoms you might be having.
• Blood Samples: Blood samples will be taken throughout the study.
o Hematology and Chemistry: These blood samples will be used to evaluate your blood counts and blood chemistry, which will help determine whether your body reacts well to the study drug and follow-up any risks and discomforts. These results will also be used to see if you are well enough to continue receiving the drug. The total amount of blood for these tests is about 15ml or 3teaspoons.
o Pregnancy Tests: If you are a woman and are able to have a baby, a blood or urine sample will be taken to make sure you are not pregnant within 7 days before the first dosing then again every 3 cycles and at end of treatment visit.
• Imaging: MRI and/or CT (*CAT scan*). Radiographic scans, which look at the status of your disease and evaluate your response to the study drug, will be performed. Your study doctor will determine which type of scan is best to assess your cancer.

Contacts

Public
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US
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Have histologically or cytologically confirmed stage IIIB (locally advanced or recurrent and not a candidate for curative therapy) or stage IV NSCLC.
2. Must meet both of the following 2 criteria:
a) Have documentation of ALK rearrangement by a positive result from any laboratory test approved by the Food and Drug Administration (FDA) (eg, the Vysis ALK Break Apart FISH [fluorescence in situ hybridization] Probe Kit or the Ventana ALK [D5F3] CDx [companion diagnostic] Assay or Foundation Medicine*s FoundationOne CDx)
or
Have documented ALK rearrangement by a different test (non-FDA-approved local lab tests) and have provided tumor sample to the central laboratory (Note: Central laboratory ALK rearrangement testing results are not required to be obtained before randomization.)
b) The patient had been treated with any 1 of the ALK tyrosine kinase inhibitors (TKIs) (alectinib, ceritinib, crizotinib) for at least 12 weeks before progression.
3. Had progressive disease while on alectinib or ceritinib (defined as no more than 1 month from last dose of alectinib or ceritinib to disease progression, as assessed by the investigator or treating physician). (Number of patients not previously treated with alectinib will be capped at 10 for every 30 patients enrolled.)
4. Had alectinib or ceritinib as the most recent ALK inhibitor therapy. Chemotherapy before or after progression on alectinib or ceritinib is allowed.
5. Have at least 1 measurable lesion per RECIST version 1.1 as assessed by the investigator.
6. Recovered from toxicities related to prior anticancer therapy to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 Grade <=1. (Note: Treatment-related alopecia or peripheral neuropathy that are

Grade >1 are allowed if deemed irreversible.)
7. Have Eastern Cooperative Oncology Group performance status <=1.
8. Have adequate organ and hematologic function.

Exclusion criteria

1. Received any prior ALK-targeted TKI other than crizotinib, alectinib, or ceritinib.
2. Received both alectinib and ceritinib.
3. Received crizotinib, alectinib, or ceritinib within 7 days of the first dose of brigatinib.
4. Previously received more than 3 regimens of systemic anticancer therapy for locally advanced or metastatic disease.
Note: A systemic anticancer therapy regimen will be counted if it is administered for at least 1 complete cycle. A new anticancer agent used as maintenance therapy will be counted as a new regimen. Neo-adjuvant or adjuvant systemic anticancer therapy will be counted as a prior regimen if disease progression/recurrence occurred within 12 months upon completion of this (neo-)adjuvant therapy.
5. Have symptomatic brain metastasis (parenchymal or leptomeningeal). Patients with asymptomatic brain metastasis or who have stable symptoms that did not require an increased dose of corticosteroids to control symptoms in the past 7 days before the first dose of brigatinib may be enrolled.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-10-2019
Enrollment:	4

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Brigatinib
Generic name:	/

Ethics review

Approved WMO Date:	01-10-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-08-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EudraCT	EUCTR2018-000635-27-NL
ClinicalTrials.gov	NCT03535740
CCMO	NL66462.078.18

Study results

Date completed: 25-01-2021

Results posted: 22-01-2025

First publication
14-01-2025