A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) versus Crizotinib in Patients with ALK-positive Advanced Lung Cancer

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The primary objective of the study is to compare the efficacy of brigatinib to that of crizotinib in ALK+ locally advanced or metastatic NSCLC patients naive to ALK inhibitors, as evidenced by PFS.The secondary objectives of the study are:1. To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50594

Source
ToetsingOnline

Brief title
ALTA 1L study

Condition

- Other condition

Synonym
ALK-positive Advanced Non-Small Cell Lung Cancer

Health condition

longaandoeningen

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.

Intervention

Keyword: anaplastic lymphoma kinase (ALK), brigatinib, crizotinib, non-small cell lung cancer (NSCLC)

Outcome measures

Primary outcome

PFS, as assessed by the BIRC, per RECIST v1.1 (Eisenhauer et al, 2009)

Secondary outcome

1. Confirmed ORR, as assessed by the BIRC, per RECIST v1.1

2. Confirmed intracranial ORR as assessed by the BIRC

3. Intracranial PFS, as assessed by the BIRC

4. OS

5. Duration of response, as assessed by the BIRC

6. Time to response, as assessed by the BIRC

7. Disease control rate, as assessed by the BIRC

8. Safety and tolerability

9. Change from baseline scores in global health status/quality of life (QOL),

assessed with the EORTC QLQ-C30 (v3.0) and time-to-deterioration in dyspnea

assessed with the EORTC QLQ-LC13 (v3.0)

Study description

Background summary

Activating gene rearrangements in anaplastic lymphoma kinase (ALK) have been identified as driver mutations in approximately 2% to 7% of patients with non-small cell lung cancer (NSCLC) (Kwak et al, 2010; Wong et al, 2009). Crizotinib (XALKORI® USPI, Pfizer, Inc.) has demonstrated clinical efficacy in ALK+ NSCLC. Results from a phase 1 study and a phase 2 single-arm study of crizotinib
demonstrated objective response rates (ORRs) of 61% and 50%, respectively (XALKORI® USPI, Pfizer, Inc.). These 2 studies served as the basis for accelerated approval of crizotinib for treatment of ALK+ advanced NSCLC in the United States (US) in 2011 and conditional marketing authorization in the European Union (EU) in 2012. The efficacy of crizotinib in ALK+ NSCLC patients has also been investigated in a randomized active-control study against chemotherapy (pemetrexed or docetaxel) (XALKORI® USPI, Pfizer, Inc.). A statistically significant improvement in progression-free survival (PFS) was observed in patients treated with crizotinib compared with patients treated with chemotherapy (hazard ratio, 0.49; 95% CI: 0.37 to 0.64; p<0.001). A median PFS of 7.7 months was seen with crizotinib versus 3.0 months with chemotherapy. Regular approval for crizotinib was granted by the US Food and Drug Administration (FDA), on the basis of this study, in 2013. In a separate randomized active-control study of crizotinib against pemetrexed-platinum doublet chemotherapy in patients with advanced previously untreated non-squamous ALK+ NSCLC, median PFS was 10.9 months in the crizotinib arm and 7.0 months in the chemotherapy arm (hazard ratio for progression or death with crizotinib, 0.45; 95% CI: 0.35 to 0.60; p<0.001) (Solomon et al, 2014). Currently, two tests are FDAapproved for detection of ALK+ NSCLC: the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit (Abbott Molecular, Inc.) and the Ventana ALK (D5F3) CDx Assay (Ventana Medical Systems, Inc.), an immunohistochemistry (IHC) assay.

Although crizotinib is an effective treatment for ALK+ NSCLC, almost half (39% and 52%, respectively) of ALK+ NSCLC patients in the two trials that supported its accelerated approval failed to achieve a response. For those patients who did respond, the benefit was relatively short with a median duration of response of 11 months (XALKORI® USPI, Pfizer, Inc.). In many patients, loss of response to crizotinib manifests as systemic progression, but in some patients the disease progresses only within the brain, possibly as a result of low central nervous system (CNS) penetration of crizotinib (Camidge et al, 2012; Costa et al, 2011).

The underlying reason for failure to achieve a response to crizotinib (primary resistance) is difficult to identify, but suboptimal potency of the agent against the targeted oncogene could be a contributing factor. The mechanisms

underlying loss of response (secondary or acquired resistance) to crizotinib are becoming more clear (Camidge et al, 2012). Emerging data suggest that an important acquired resistance mechanism is the emergence of point mutations in the kinase domain of ALK (Katayama et al, 2012). Mutations that confer resistance to crizotinib (such as the gatekeeper mutant L1196M, as well as L1152R, G1269A, S1206Y, F1174L, D1203N, C1156Y, T1151Tins, and G1202R mutations) may act by reducing the
binding affinity of crizotinib to ALK (Bang, 2012).

In some patients, loss of response to crizotinib may also have a pharmacologic basis, with inadequate drug exposure resulting from dose modifications, or changes in drug metabolism or transport over time. In all of these scenarios, a rational approach to overcoming resistance is the use of a more potent ALK inhibitor with a broader therapeutic window that suppresses the emergence of resistance mutations in ALK
and that can also achieve deep and prolonged target inhibition both systemically and in the CNS (for patients with brain metastases).

Brigatinib is a novel, synthetic, orally-active ALK tyrosine kinase inhibitor (TKI) discovered and developed at ARIAD Pharmaceuticals, Inc. Brigatinib has demonstrated potent in-vitro inhibitory activity against activated ALK (approximately 10-fold more potent than crizotinib) and pan-inhibitory activity against all 17 ALK resistance mutants identified to date, including the L1196M gatekeeper mutation and the G1202R mutation.

Study objective

The primary objective of the study is to compare the efficacy of brigatinib to that of crizotinib in ALK+ locally advanced or metastatic NSCLC patients naive to ALK inhibitors, as evidenced by PFS.

The secondary objectives of the study are:
1. To compare the efficacy of brigatinib to that of crizotinib, as evidenced by confirmed ORR, time to/duration of response, disease control rate (DCR), and Overall Survival (OS)
2. To compare the efficacy in the CNS of brigatinib to that of crizotinib, as evidenced by intracranial response and intracranial PFS in those patients with intracranial CNS metastases at baseline
3. To assess the safety and tolerability of brigatinib in comparison with crizotinib
4. To determine pharmacokinetic (PK) parameters of brigatinib through population PK modeling
5. To assess patient-reported symptoms and health-related quality of life (HRQoL) with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (v3.0) and its lung cancer module, QLQ-LC13 (v3.0) in patients treated with brigatinib compared to those treated with crizotinib

The exploratory objectives of the study are:
1. To assess confirmed ORR on brigatinib in patients who crossover to brigatinib from Arm B (crizotinib); and to assess PFS, from the first dose of brigatinib, in patients who crossover to brigatinib from Arm B
2. To explore the relationship of brigatinib exposure with both efficacy and safety
3. To explore the molecular determinants of efficacy and safety for brigatinib and crizotinib

Study design

Patients will be randomized to receive brigatinib or crizotinib in a 1:1 fashion. Patients will be stratified by the presence of intracranial CNS metastases at baseline (Yes versus No) and prior chemotherapy use for locally advanced or metastatic disease (Yes versus No). For the purposes of stratification, prior chemotherapy is defined as completion of *1 full cycle of chemotherapy in the locally advanced or metastatic setting.

Arm A (brigatinib):
Brigatinib will be administered orally at a dose of 90 mg QD for 7 days, then 180 mg QD, continuously, with or without food. Patients will take the prescribed dose with water (recommended 240 mL).

Arm B (crizotinib):
Crizotinib will be administered as 250 mg orally BID, with or without food. Patients will take the prescribed dose with water (recommended 240 mL).

Dose Modifications
Dose interruptions or reductions should be implemented for patients who experience treatment-related AEs, based on the clinical judgment of the investigator. Criteria for dose modifications of brigatinib for drug-related toxicity are described in the protocol.

The European Medicines Agency (EMA) Summary of Product Characteristics (SmPC) for crizotinib (XALKORI® SmPC, Pfizer, Inc.) will be used as a guideline for dose modification of patients in the crizotinib arm and is detailed in the protocol

Intervention

Not applicable

Study burden and risks

See protocolsection 11, page 38 till 51

Contacts

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US
Scientific
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Landsdowne Street 40
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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 definitive multimodality therapy) or stage IV NSCLC.
2. Patient must meet one of the following two criteria:
a. Have documentation of ALK rearrangement by a positive result from the Vysis® ALK Break-Apart fluorescence in situ hybridization (FISH) Probe Kit or the Ventana ALK (D5F3) CDx Assay. The test must have been performed according to the product*s instructions for use (IFU).
b. Have documented ALK rearrangement by a different test and adequate tissue available for central laboratory testing by an FDA-approved test. Confirmation

of central test positivity is not required prior to randomization.
3. Have sufficient tumor tissue available for central analysis
4. Have at least 1 measurable (i.e., target) lesion per RECIST v1.1
5. Recovered from toxicities related to prior anticancer therapy to NCI CTCAE v 4.0 grade *1. Note: treatment-related alopecia or peripheral neuropathy that are grade >1 are allowed if deemed irreversible
6. Are a male or female patient *18 years old.
7. Have adequate organ function, as defined by the study protocol
8. Have Eastern Cooperative Oncology Group (ECOG) performance status *2
9. Have normal QT interval on screening ECG evaluation, defined as QT interval corrected (Fridericia) (QTcF) of *450 milliseconds (msec) in males or *470 msec in females.
10. For female patients of childbearing potential, have a negative pregnancy test
documented prior to randomization.
11. For female and male patients who are fertile, agree to use a highly effective
form of contraception with their sexual partner during the dosing period and for a period of at least 4 months after the end of treatment with brigatinib and at least 3 months after the end of treatment with crizotinib, as defined by the study protocol
12. Provide signed and dated informed consent indicating that the patient has been informed of all pertinent aspects of the study, including the potential risks, and is willingly participating.
13. Have the willingness and ability to comply with scheduled visit and study procedures.

Exclusion criteria

1. Previously received an investigational antineoplastic agent for NSCLC.
2. Previously received any prior TKI, including ALK-targeted TKIs.
3. Previously received more than 1 regimen of systemic anticancer therapy for locally advanced or metastatic disease.
4. Received chemotherapy or radiation within 14 days of first dose of study drug, except stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT).
5. Received anti-neoplastic monoclonal antibodies within 30 days of the first dose of study drug.
6. Had major surgery within 30 days of the first dose of study drug, minor surgical procedures such as catheter placement or minimally invasive biopsies are allowed.
7. Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated non-melanoma skin cancer or cervical cancer in situ; definitively treated non-metastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years

elapsed since the diagnosis of the other primary malignancy.
8. Have symptomatic CNS metastases (parenchymal or leptomeningeal) at screening or asymptomatic disease requiring an increasing dose of corticosteroids to control symptoms within 7 days prior to randomization.
9. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed.
10. Be pregnant, planning a pregnancy, or breastfeeding
11. Have significant, uncontrolled, or active cardiovascular disease as defined by the study protocol
12. Have uncontrolled hypertension.
13. Have a history or the presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis.
14. Have an ongoing or active infection
15. Have a known history of human immunodeficiency virus (HIV) infection.
16. Have a known or suspected hypersensitivity to brigatinib or its excipients and/or crizotinib or its excipients.
17. Have malabsorption syndrome or other gastrointestinal (GI) illness or condition
18. Have any condition or illness that, in the opinion of the investigator, would
compromise patient safety or interfere with the evaluation of the study drug.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-10-2016

Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	For Brigatinib not available yet
Generic name:	For Brigatinib not available yet
Product type:	Medicine
Brand name:	Xalkori
Generic name:	Xalkori
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-04-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-07-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	14-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-10-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	19-11-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2015-003447-19-NL
ClinicalTrials.gov	NCT02737501
CCMO	NL57216.042.16