Phase 3, Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Published: 21-07-2016
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-513454-29-00 check the CTIS register for the current data. Primary:To evaluate the efficacy and safety of Ensartinib vs. crizotinib in patients with ALK-positive NSCLC that have received up to 1...

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

Summary

ID

NL-OMON54615

Source
ToetsingOnline

Brief title
XALT3

Condition

- Other condition

Synonym
ALK-positive Non-Small Cell Lung Cancer

Health condition

longkanker

Research involving

Human

Sponsors and support

Primary sponsor: Xcovery Holdings Inc.
Source(s) of monetary or material Support: Xcovery Holding Company;LLC

Intervention

Keyword: Anaplastic Lymphoma Kinase, Ensartinib, Non-Small Cell Lung Cancer, Phase III

Outcome measures

Primary outcome

Progression-free survival (PFS) as assessed by independent radiology review based on RECIST v. 1.1 criteria.

Secondary outcome

• Key Secondary Efficacy Endpoints: Overall survival, CNS response rate (based on IRR), time to CNS progression (based on IRR), objective response rate (based on IRR)

• Other Secondary Efficacy Endpoints: PFS (based on investigator assessment), ORR (based on investigator assessment), time to response (based on investigator assessment and IRR), duration of response (based on investigator assessment and IRR), CNS response rate (based on investigator assessment), time to CNS progression (based on investigator assessment)..

Exploratory:

Patient reported time to deterioration (TTD) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale (LCSS), patient reported healthrelated quality of life (HRQoL) as measured by the EORTC C30/LC13 QoL

questionnaire and LCSS, pharmacodynamic (PD) and possible pharmacogenetic (PG)

assessments.

Study description

Background summary

The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is aberrant in a variety of malignancies. ALK was originally discovered in anaplastic large cell lymphoma (ALCL) as part of a chromosomal translocation t(2,5), which fuses the C-terminal kinase domain of ALK
encoded on chromosome 2p23 to the N-terminus of nucleophosmin (NPM) on chromosome 5q35 (Morris et al. 1994). Subsequently, a variety of ALK fusion proteins have been found in multiple malignancies, including inflammatory myofibroblastic tumor (IMT) (Lawrence et al. 2000) and non-small cell lung cancer (NSCLC) (Soda et al. 2007; Choi et al. 2008; Koivunen et al. 2008; Takeuchi et al. 2008; Takeuchi et al. 2009; Wong et al. 2009; Horn and Pao 2009; Rikova et al. 2007). All ALK fusions tested biologically to date have demonstrated gain of
function properties (Morris et al. 1994; Soda et al. 2007; Koivunen et al. 2008; Takeuchi et al. 2009). Activating mutations in wild-type ALK have also been identified in both familial and sporadic neuroblastoma. Most of these activating mutations occur within the tyrosine kinase
domain and are transforming in vitro and in vivo (Mosse et al. 2008; George et al 2008; Janoueix-Leorosey et al. 2008; Chen et al 2008). Importantly, the activity of cancer-specific ALK variants is required for tumor maintenance. Thus, ALK mutants can serve as *Achilles
heels* to be exploited therapeutically. Multiple preclinical studies have shown that specific small molecule ALK tyrosine kinase inhibitors (TKIs) can delay tumor growth and/or induce tumor regression in xenograft and transgenic models (Soda et al. 2007; Choi et al. 2008; Koivunen et
al. 2008; Sabbatini et al. 2009). Based on such promising nonclinical studies, ALK TKIs entered into clinical trials. The first
agent in humans was crizotinib (Xalkori®, Pfizer, also known as PF-2341066 or PF-1066), an orally available small molecule ATP-mimetic compound that was approved for commercial use in the U.S. in August 2011 for the treatment of metastatic NSCLC that is ALK-positive.
Crizotinib was originally designed as a MET inhibitor but was recognized to have *off-target* anti-ALK activity (Zou et al. 2007). Strikingly, in a Phase 1 study, patients with ALK fusionpositive NSCLC demonstrated a >60% radiographic response rate (Bang et al. 2008). Crizotinib
has been shown to be superior to chemotherapy in the first and second line treatment of patients with ALK fusion-positive NSCLC. By contrast, chemotherapy

response rates are <10% in previously treated patients with unselected NSCLC (Hanna et al. 2004). Several other ALK
TKIs have entered into clinical trials, with ceritinib (Zykadia*, Novartis, also known as LDK378) being approved in the U.S. in 2014 for use in patients that have progressed on or are intolerant to crizotinib.

Xcovery Holding Company, LLC (the Sponsor) has developed X-396, a novel potent and specific ALK inhibitor with potential therapeutic relevance. In in vitro and in vivo nonclinical studies, X-396 exhibited a favorable effectiveness profile, including anti-tumor activity against multiple ALK variants including some that are resistant or become resistant to crizotinib.

Study objective

This study has been transitioned to CTIS with ID 2024-513454-29-00 check the CTIS register for the current data.

Primary:
To evaluate the efficacy and safety of Ensartinib vs. crizotinib in patients with ALK-positive NSCLC that have received up to 1 prior chemotherapy regimen and no prior ALK tyrosine kinase inhibitor (TKI).

Secondary:
To obtain additional pharmacokinetic (PK) data on Ensartinib from sparse PK sampling from patients at selected sites.
To compare the quality of life (QoL) in patients receiving Ensartinib vs. crizotinib

Exploratory:
To evaluate the status of exploratory biomarkers and correlate with clinical outcome.
To obtain germline DNA samples for possible pharmacogenetic analysis in the event that outliers with respect to efficacy, tolerability/safety, or exposure are identified.

Study design

A Phase 3 open-label, randomized study of the ALK inhibitors Ensartinib and crizotinib given as single agents.Patients will be randomized 1:1.

Intervention

Not applicable.

Study burden and risks

See Protocol Section 9, page 31 up to and including 35 (and Appendix E).
Patient diary must be completed.

Contacts

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Xcovery Holdings Inc.

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Scientific
Xcovery Holdings Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1.Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive by an FDA-approved assay performed centrally. Patients must be ALK positive by local test prior to submitting tissue to the central lab. Randomization will occur after ALK positive confirmation is received from the central lab. Patients may have received up to 1 prior chemotherapy regimen for mestatic disease , which may also include maintenance therapy.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0

to 2.
3. Life expectancy of at least 12 weeks.
4. Ability to swallow and retain oral medication.
5. Adequate organ system function, defined as follows:
a. Absolute neutrophil count (ANC) >=1.5 x 109/L
b. Platelets >=100 x 109/L
c. Hemoglobin >=9 g/dL (>=90 g/L) Note that transfusions are allowed to meet the required hemoglobin level.
d. Total bilirubin <=1.5 times the upper limit of normal (ULN)
e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=2.5 x ULN if no liver involvement or <=5 x ULN with liver involvement.
f. Creatinine <=1.5 x ULN. If >1.5 x ULN, patient may still be eligible if calculated creatinine clearance >=50 mL/min (0.83 mL/s) as calculated by the Cockcroft-Gault method.
6. Brain metastases allowed if asymptomatic at study baseline. Patients with untreated brain metastases must not be on corticosteroids. If patients have neurological symptoms or signs due to CNS metastases, patients need to complete whole brain radiation or focal treatment at least 14 days
before start of study treatment and be asymptomatic on stable or decreasing doses of corticosteroids at baseline.
7.Men with partners of childbearing potential willing to use adequate contraceptive measures during the study and for 90 days after the last dose of study medication.
8.Women who are not of child-bearing potential, and women of childbearing potential who agree to use adequate contraceptive measures during the study and for 90 days after the last dose of study medication, and who have a negative serum or urine pregnancy test within 1 week prior to initial trial treatment.
9. Patients must be >=18 years of age.
10. Patients must have measurable disease per RECIST v. 1.1.
11. Patients must be ALK-positive by IHC. Testing will be done centrally; however, patients will be allowed to enroll based on local results (positive by FISH or IHC), if available.
12. Willingness and ability to comply with the trial and follow-up procedures.
13. Ability to understand the nature of this trial and give written informed consent.

Exclusion criteria

1. Patients that have previously received an ALK TKI or PD-1 or PD-L1 therapy, and patients currently receiving cancer therapy (i.e., other targeted therapies, chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization).
2. Use of an investigational drug within 21 days prior to the first dose of study drug. Note that to be eligible, any drug-related toxicity should have recovered to Grade 1 or less, with the exception of alopecia.

3. Any chemotherapy within 4 weeks, or major surgery or radiotherapy within the last 14 days.
4. Patients with primary CNS tumors and leptomeningeal disease are ineligible.
5. Patients with a previous malignancy within the past 3 years (other than curatively treated basal cell carcinoma of the skin, in situ carcinoma of the cervix, or any cancer that is considered to be cured and have no impact on PFS and OS for the current NSCLC).
6. Concomitant systematic use of anti-cancer herbal medications. These should be stopped prior to study entry.
7.Patients receiving
a. strong CYP3A inhibitors (including, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, grapefruit, grapefruit juice)
b. strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort)
c. CYP3A substrates with narrow therapeutic window (including, but not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).
8. Women who are pregnant or breastfeeding.
9. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of study medications.
10. Patients at risk for GI perforation
11. Clinically significant cardiovascular disease including:
a. QTcF interval >450 ms for men and >470 ms for woman, symptomatic bradycardia <45 beats per minute or other significant ECG abnormalities in the investigator's opinion.
b. Clinically uncontrolled hypertension in the investigator's opinion (e.g., blood pressure >160/100 mmHg; note that isolated elevated readings considered to not be indicative of uncontrolled hypertension are allowed).
The following within 6 months prior to Cycle 1 Day 1:
a. Congestive heart failure (New York Heart Class III or IV).
b. Arrhythmia or conduction abnormality requiring medication. Note: patients with atrial fibrillation/flutter controlled by medication and arrhythmias controlled by pacemakers are eligible.
c. Severe/unstable angina, coronary artery/peripheral bypass graft, or myocardial infarction.
d. Cerebrovascular accident or transient ischemia.
12. Patients who are immunosuppressed (including known HIV infection), have a serious active infection at the time of treatment, have interstitial lung disease/pneumonitis, or have any serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. Patients with controlled hepatitis C, in the investigator's opinion, are allowed.
Patients with known hepatitis B must be HBeAg and HB viral DNA negative for enrollment. Note that, because of the high prevalence, all patients in the Asia-Pacific region (except Australia, New Zealand, and Japan) must be tested

and, if HBsAg positive, must be HBeAg and HB viral DNA negative for enrollment.
13. Known hypersensitivity to tartrazine, a dye used in ensartinib 100 mg capsule.
14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
15. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol or would impart excessive risk associated with study participation that would make it inappropriate for the patient to be enrolled.
16. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-07-2017
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	For X-396 (Ensartinib) not available yet
Generic name:	For X-396 (Ensartinib) not available yet
Product type:	Medicine
Brand name:	Xalkori
Generic name:	Xalkori

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-07-2016
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-03-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-11-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-11-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	08-03-2018
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-04-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-09-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-03-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-04-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-04-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	09-09-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-09-2020
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-05-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	01-10-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-10-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-11-2022
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-03-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-04-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-11-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-12-2023
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	CTIS2024-513454-29-00
EudraCT	EUCTR2015-004147-40-NL
CCMO	NL58390.068.16