Cross-tumoral Phase 2 clinical trial exploring Crizotinib (PF-02341066) in patients with advanced tumours induced by causal alterations of either ALK or MET.

Published: 27-07-2012
Last updated: 01-05-2024

Primary objective* To study the antitumor activity and safety of crizotinib across predefined tumor types in patients whose tumors are harboring specific alterations in ALK and/or METSecondary objectives* To study the specificity of the kinase...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON55860

Source
ToetsingOnline

Brief title
CREATE

Condition

- Haematological disorders NEC
- Miscellaneous and site unspecified neoplasms benign

Synonym
Anaplastic large cell lymphoma; Inflammatory myofibroblastic tumor; Papillary renal cell carcinoma type 1; Alveolar soft part sarcoma; Clear cell sarcoma; Alveolar rhabdomyosarcoma

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: EORTC,Pfizer

Intervention

Keyword: ALK MET alteration, Crizotinib, Crosstumoral, Phase II

Outcome measures

Primary outcome

Primary objective

* To study the antitumor activity and safety of crizotinib across predefined tumor types in patients whose tumors are harboring specific alterations in ALK and/or MET

Secondary objectives

* To study the specificity of the kinase inhibitor for tumors in all cohorts by explorative comparison of treatment results in patients with the same disease type with and without alterations in ALK and/or MET pathways (*ALK/MET+* and *ALK/MET-*sub-cohorts).

* To investigate sensitive and reliable methodologies for patient screening for such defects, to be potentially cross-validated and further developed by an accredited laboratory in later steps, based on prospectively collected biological material from this trial.

* To explore the potential value of selected biomarkers to study the pharmacological effects of crizotinib, to be used later in the context of future trials.

* To explore whether molecularly driven, high quality multi-tumor screening Phase II trials are feasible in a multiinstitutional, multidisciplinary setting, when screening and treatment are performed by EORTC sites(+/- additional selected sites).

Secondary outcome

Secondary objectives

* To study the specificity of the kinase inhibitor for tumors in all cohorts by explorative comparison of treatment results in patients with the same disease type with and without alterations in ALK and/or MET pathways (*ALK/MET+* and *ALK/MET-*sub-cohorts).

* To investigate sensitive and reliable methodologies for patient screening for such defects, to be potentially cross-validated and further developed by an accredited laboratory in later steps, based on prospectively collected biological material from this trial.

* To explore the potential value of selected biomarkers to study the pharmacological effects of crizotinib, to be used later in the context of future trials.

* To explore whether molecularly driven, high quality multi-tumor screening Phase II trials are feasible in a multiinstitutional, multidisciplinary setting, when screening and treatment are performed by EORTC sites(+/- additional selected sites).

Study description

Background summary

This clinical trial is a biomarker-driven multi-tumor Phase II multicentric trial investigating the activity of the single agent crizotinib (Xalkori®).
The primary objective of this clinical trial is to study the antitumor activity and the safety of crizotinib across predefined tumor types in patients whose tumors are harboring specific alterations in Anaplastic Lymphoma Kinase (ALK) and/or MET (hepatocyte growth factor receptor).
The study will comprise six tumor-specific cohorts, with two subcohorts per tumor type: those with and those without specific pathway alterations.
The six tumor types are:
1. Anaplastic large cell lymphoma (ALCL)
ALCL is a rare variant of Non-Hodgkin*s lymphoma associated with ALK alterations in 80-90% of cases diagnosed in adolescents and young adults.
2. Inflammatory myofibroblastic tumor (IMFT)
IMFT is a distinctive mesenchymal neoplasm characterized by a spindle-cell proliferation with an inflammatory infiltrate. Rearrangements involving the ALK locus on chromosome 2p23 have been documented in approximately 50% of IMFTs. Several ALK fusion proteins are found in IMFT and induce transformation in cell lines and animal models, a finding that suggests that ALK rearrangement may define a subgroup of IMFTs that is sensitive to targeted kinase inhibition.
3. Papillary renal cell carcinoma type 1 (PRCC)
PRCC occurs in sporadic and hereditary forms, accounting for 10 to 15% of carcinomas of the renal tubular epithelium. Recent molecular analysis identified missense mutations in the tyrosine kinase domain of the MET proto-oncogene in hereditary and 5 to 13% of sporadic PRCCs.
4. Alveolar soft part sarcoma (ASPS)
ASPS is a clinically and morphologically distinct soft tissue sarcoma. It is an uncommon tumor and uniformly malignant. ASPS is characterized by the presence of a specific chromosomal translocation encoding the chimeric transcription factor (ASPL-TFE3) that activates expression of MET. The high expression of MET in ASPL-TFE3 (+) ASPS supports the potential role of targeted agents against MET in this rare and very chemoresistant tumor.
5. Clear cell sarcoma (CCSA)
CCSA is an aggressive soft tissue sarcoma that typically develops in the tendons and aponeuroses of children and young adults. MET expression is critical for CCSA invasion, chemotaxis and survival.
6. Alveolar rhabdomyosarcoma (ARMS)
Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood and does also occur in adults. MET is highly expressed in ARMS cell lines established from human tumors and HGF/SF promotes their motility and resistance to chemotherapy. In addition to the role of MET, ALK seems to have importance in ARMS as well. Immunohistochemical staining for ALK has been observed in ARMS.
For each tumor subtype described above, two subcohorts of patients will be enrolled:
• those with specific pathway alterations (*ALK/MET+*).

• those without specific pathway alterations (*ALK/MET-*).
A maximum of 35 patients for each of the 6 *ALK/MET+* subcohorts will be treated. In theory a maximum of 35 patients for each of the 6 *ALK/MET-* subcohorts will be treated, if none of the stopping rules are met but it will not be mandatory to complete the *ALK/MET-* subcohorts.
The number of patients who have to be screened in order to recruit 35 ALK/MET+ patients depends on the prevalence of the according pathway alterations. The number of patients who have to be screened to accrue 35 patients based on prevalence estimates varying from 40% to 60% for all 6 * ALK/MET +* sub-cohorts is approximately 378-582 patients.
The minimal age for recruited patients will be 15 years old; no upper age limit is fixed.

Study objective

Primary objective
* To study the antitumor activity and safety of crizotinib across predefined tumor types in patients whose tumors are harboring specific alterations in ALK and/or MET
Secondary objectives
* To study the specificity of the kinase inhibitor for tumors in all cohorts by explorative comparison of treatment results in patients with the same disease type with and without alterations in ALK and/or MET pathways (*ALK/MET+* and *ALK/MET-*sub-cohorts).
* To investigate sensitive and reliable methodologies for patient screening for such defects, to be potentially cross-validated and further developed by an accredited laboratory in later steps, based on prospectively collected biological material from this trial.
* To explore the potential value of selected biomarkers to study the pharmacological effects of crizotinib, to be used later in the context of future trials.
* To explore whether molecularly driven, high quality multi-tumor screening Phase II trials are feasible in a multiinstitutional, multidisciplinary setting, when screening and treatment are performed by EORTC sites(+/- additional selected sites).

Study design

This is a biomarker-driven multi-tumor single agent Phase II trial. The study will assess the efficacy of crizotinib in a variety of tumors with specific alterations in either ALK and/or MET. The patient population will include patients with tumors harboring specific alterations leading to ALK and/or MET activation. The trial will also include patients with the same tumor types without specific ALK or MET alterations.

Intervention

treatment with crizotinib until disease progression

Study burden and risks

Potential side effect of crizotinib
Baseline/screening evaluations, safety and efficacy evaluations as described in the protocol

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue du Mounier 83/11
Brussel 1200
BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue du Mounier 83/11
Brussel 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Step 1 registration:
* Local diagnosis of locally advanced and/or metastatic malignant tumor (ALCL,

IMFT, PRCC, ASPS, CCSA, ARMS) deemed incurable by conventional surgery, radiotherapy, systemic therapy or any other means.
* Mandatory availability for shipment of formalin-fixed, paraffinembedded, tumor-containing, non-returnable tissue blocks from primary tumor and/or metastatic site (Slides not accepted). Information on previous histopathology reports and previous molecular analysis will be
entered in an eCRF, to accompany the tissue samples.
* Written informed consent for central collection of tissue block and any other trial-specific procedures must be obtained from the patient allowing for collection storage and analysis of tissue and screening procedures prior to registration.
Step 2 histopathology central confirmation:
* Confirmation of receipt of tissue block and accompanying required local information, and confirmation that tissue block contains tumor tissue (quality assurance) by central biorepository through EORTC, as well as central pathology confirmation, are required before starting the
patient screening (step 3) according to chapter 6.4.
Step 3 enrollment:
* Measurable disease according to RECIST 1.1 with target lesion of at least 20 mm (or 10 mm on spiral CT scans) and presence of at least one RECIST-measurable lesion outside of a previously radiated field or potential palliative
irradiation fields.
* Patients with brain metastases are eligible if treated and/or neurologically stable with no ongoing requirement for corticosteroids (off steroids for at least 2 weeks) and not taking contraindicated
medications . Absence of spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.
* Minimum age 1 years, no upper age limit.
* Eastern Cooperative Oncology Group (ECOG) performance status 0-2, or Lansky play scale >= 50 for children aged 1 to 12 yo. (Appendix F).
* Adequate hematological function: ANC >= 1 x 109/L, platelets >= 30 x 109/L and hemoglobin >= 8 g/dL.
* Adequate renal function:
A) for patients up to 21 years old: The Schwartz formula should be used for Clearance Creatinine (mL/min/1.73 m2= F x Height (cm) x 88,4/creatinine (blood) in µmol/L. ClCr of 80-140 mL/min/1.73 m2 is considered as normal range.
- F = 0.55 for boys 1-15 yo
- F = 0.70 for boys 16-21 yo
- F = 0.55 for girls 1-21 yo
B) For patients 21 years or older:
serum creatinine <= 2 x ULN.
* Adequate liver function: Bilirubin <= 1.5 x ULN unless due to Gilbert's syndrome (status of the disease documented by repeated laboratory values with slight increase in bilirubin without any other known. AST and ALT <= 2.5 x ULN in the absence of liver metastases and metastases <= 5 x UNL if liver function abnormalities are due to the underlying malignancy.
* Note: Crizotinib should be avoided in patients with congenital long QT

syndrome
* Machine-read ECG with QTcF interval <470 msec.
* Able to swallow capsules.
* Women of child bearing potential with negative serum pregnancy test
* All patients of childbearing/reproductive potential using adequate birth control
Disease specific inclusion criteria for patients with anaplastic large cell lymphoma (ALCL)
* Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or advanced disease.
* Patient must have received previous systemic chemotherapy (usually a CHOP-like multidrug combination, if not medically contraindicated, with or without monoclonal antibodies), and may not qualify for further conventional therapy with curative intent.
* No pretreatment limitations (including autologous or allogeneic stem cell- or bone marrow transplantation), provided all other patient selection criteria are met.
Disease-specific inclusion criteria for patients with inflammatory myofibroblastic tumor (IMFT), papillary renal cell carcinoma type 1 (PRCC),clear cell sarcoma (CCSA),alveolar soft part sarcoma (ASPS), alveolar rhabdomyosarcoma (ARMS)
* Patient may have received previous systemic treatment, surgery and/or radiotherapy for localized, locally advanced or metastatic disease.
* No mandatory pretreatment.
* No pretreatment limitations, provided all other patient selection criteria are met.

Exclusion criteria

Malignant meningitis or leptomeningeal disease.
* Any previous systemic anticancer therapy in the last 4 weeks prior to initiation of study medication.
* Treatment with any other investigational drug within the past 4 weeks or within less than 4 half-life times of the investigational drug before treatment with crizotinib (whatever is the longest period).
* Prior therapy directly targeting ALK and/or MET, Previous treatment with crizotinib.
* Major surgery in past 4 weeks prior to initiation of study medication.
* Prior palliative radiotherapy 24 hrs prior to initiation of study medication, and minor surgical procedures two weeks prior to the initiation of study medication.
* Other previous and active malignancy for the last three years with the exception of non-melanoma skin cancer, localized cervical cancer, localized and presumably cured prostate cancer or adequately treated basal or squamous cell skin carcinoma.

* Laboratory abnormalities that would impart, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration.
* All related adverse events from previous therapies must have recovered to <= Grade 1 (except alopecia). No persistence of adverse events from prior anti-cancer therapy deemed clinically relevant.
* Acute or chronic severe gastrointestinal conditions such as diarrhea or ulcer.
* Within the three months prior to starting study treatment, no myocardial infarction, no severe/unstable angina, no coronary/peripheral artery bypass graft, congestive heart failure or and no cerebrovascular accident including transient ischemic attack.
* Current congestive heart failure.
* Ongoing cardiac dysrhythmias of NCI CTCAE Grade >= 2.* Uncontrolled atrial fibrillation of any grade.
* History of extensive disseminated/bilateral or known 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, but not history of prior radiation pneumonitis.
* Concurrent use of drugs or foods that are known strong CYP3A4 inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit or grapefruit juice (refer to section 5.6). The topical use of these medications (if appropriate), such as 2% ketoconazole cream, may be allowed.
* Concurrent use of drugs that are known potent CYP3A4 inducers, within 12 days prior to first dose of crizotinib including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort (refer to section 5.6).
* Use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to pimozide, dihydroergotamine, ergotamine, astemizole, cisapride, and terfenadine (refer to section 5.6).
* Other severe acute or chronic medical conditions including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric conditions or end stage renal disease on hemodialysis or laboratory abnormalities that would impact, in the judgment of the investigator and/or sponsor, excess risk associated with study participation or study drug administration, and which would, therefore, make the patient inappropriate for study entry.
* Female subjects who are breast feeding
* Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-04-2013
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Crizotinib
Generic name:	Crizotinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	27-07-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	22-04-2013
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	24-09-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-05-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-09-2015
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-01-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	21-08-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	04-11-2019
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-07-2020
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	22-02-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	07-04-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2011-001988-52-NL
ClinicalTrials.gov	NCT01524926
CCMO	NL40334.058.12