PHASE 3, RANDOMIZED, OPEN-LABEL STUDY OF THE EFFICACY AND SAFETY OF CRIZOTINIB VERSUS PEMETREXED/CISPLATIN OR PEMETREXED/CARBOPLATIN IN PREVIOUSLY UNTREATED PATIENTS WITH NON-SQUAMOUS CARCINOMA OF THE LUNG HARBORING A TRANSLOCATION OR INVERSION EVENT INVOLVING THE ANAPLASTIC;LYMPHOMA KINASE (ALK) GENE LOCUS

Published: 14-06-2011
Last updated: 27-04-2024

To demonstrate that crizotinib (Arm A) is superior to first-line chemotherapy, pemetrexed/cisplatin or pemetrexed/carboplatin (Arm B), in prolonging PFS in patients with advanced non-squamous NSCLC whose tumors harbor a translocation or inversion...

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

Summary

ID

NL-OMON38269

Source
ToetsingOnline

Brief title
A8081014/PROFILE-1014

Condition

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

Synonym
Lung cancer, non-small cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ALK positive, Crizotinib, NSCLC, open-label

Outcome measures

Primary outcome

PFS based on RECIST version 1.1 (progression of disease documented by

independent radiology laboratory).

Secondary outcome

* ORR (documented by independent radiology laboratory), OS at 6 months and 1

year, OS and DR.

* Type, incidence, severity, seriousness and relationship to study medications

of adverse events (AE) and any laboratory abnormalities.

* Plasma concentrations of crizotinib (including its active moieties, if

appropriate).

* Proportion of patients with each of the ALK fusion variants of the EML4-ALK

fusion.

* Time to deterioration in pain, dyspnea, or cough patient reported disease

symptoms.

* HRQoL, disease/treatment-related symptoms and general health status.

* HCRU with respect to hospitalizations and concomitant medication use for

select adverse events (eg, hematologic events).

Study description

Background summary

Non-small cell lung cancer (NSCLC) is the most common fatal malignancy in the United States accounting for nearly 30% of all cancer related deaths, and a frequent cause of mortality throughout the world. The majority of patients with NSCLC present with inoperable locally advanced (Stage IIIB) or metastatic (Stage IV) disease for which no curative treatment is available.

ALK gene rearrangements, recently described in NSCLC, offer an additional molecularly defined subgroup of lung cancer patients in which to explore the benefit of targeted therapy in a specific patient population compared to standard first-line chemotherapy.

Crizotinib (PF-02341066) is a selective ATP-competitive small-molecule inhibitor of ALK and c-Met/Hepatocyte Growth Factor Receptor (HGFR) tyrosine kinases and their oncogenic variants (eg, ALK fusion proteins or c-Met/HGFR mutant variants). Consistent with these mechanisms of action, crizotinib dose-dependently inhibits phosphorylation and kinase target dependent functions of ALK, c-Met/HGFR, and selected variants in tumor cells both in vitro and in vivo.

Study objective

To demonstrate that crizotinib (Arm A) is superior to first-line chemotherapy, pemetrexed/cisplatin or pemetrexed/carboplatin (Arm B), in prolonging PFS in patients with advanced non-squamous NSCLC whose tumors harbor a translocation or inversion event involving the ALK gene locus.

Study design

This is an open-label, multi-center, randomized Phase 3 efficacy and safety study of crizotinib versus first-line chemotherapy, ie, pemetrexed/cisplatin or

pemetrexed/carboplatin. A total of 334 patients will be randomized in a 1:1 ratio to receive crizotinib (Arm A) or chemotherapy (pemetrexed/cisplatin or pemetrexed/carboplatin; Arm B). The choice of the platin chemotherapy will be made by the investigator.

The randomization will be stratified by ECOG performance status (0-1 vs 2), race (Asian versus Non-Asian) and presence of brain metastases (presence or absence). Each treatment cycle is defined as 3 weeks.

Intervention

Patients will be assigned (by parallel assignment) to receive crizotinib or chemotherapy.
Crizotinib, 250 mg BID, will be administered orally at the same time on a continuous schedule, ie, no break in crizotinib dosing. Chemotherapy will be repeated every 3 weeks for a maximum of 6 cycles unless patient*s refusal to continue on study treatment or the appearance of unacceptable treatment-related toxicity or disease progression.

Study burden and risks

Any research has some risks of adverse effects. These effects may be mild or serious. In some cases, these effects can be long lasting, or permanent, and may even be life threatening.

Frequent or important drug related side effects reported by patients taking the investigational product crizotinib include nausea and vomiting (more than 30 % of the patients) and less common diarrhea and fatigue (10-29% of patients).
For pemetrexed, the most commonly experienced side effects are a low white blood cell count, a low red blood cell count, fatigue, nausea, vomiting, constipation, loss of appetite, shortness of breath and chest pain.
Side effects from cisplatin are common and include: thinned or brittle hair, loss of appetite or weight, diarrhea, nausea and vomiting, change in taste, numbness or tingling in the fingertips and toes.
Side effects from carboplatin include: constipation, diarrhea, hair loss, loss of appetite, nausea, stomach pain, vomiting, weakness.

Contacts

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Scientific
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East 42nd Street 235
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically or cytologically proven diagnosis of locally advanced not suitable for local treatment, recurrent or metastatic non squamous non small cell carcinoma of the lung.;2. Positive for translocation or inversion events involving the ALK gene locus (eg, resulting in EML4-ALK fusion) as determined by an ALK break apart FISH assay and defined by an increase in the distance between 5* and 3* ALK probes or the loss of the 5* probe.;3. No prior systemic treatment for locally advanced or metastatic disease (exception below):;- Prior adjuvant chemotherapy for Stage I-III or combined modality chemotherapy-radiation for locally advanced disease allowed if completed >12 months prior to documented disease progression.;4. Patients with brain metastases are only eligible if treated and neurologically stable with no ongoing requirement for corticosteroids, eg, dexamethasone, for at least 2 weeks and are not taking medications contraindicated in Exclusion Criteria # 12-14 (in the protocol).;5. Any major surgeries must have been completed at least 4 weeks prior to initiation of study medication. Any prior radiation (except palliative)or minor surgeries/ procedures must have been completed at least 2 weeks prior to the initiation of study medication. Palliative radiation (*10 fractions) must have completed 48 hrs prior to crizotinib therapy commencing. Any acute toxicity must have recovered to * Grade 1 (except alopecia).;6. Tumors must have measurable disease as per RECIST;7. Female or male, 18 years of age or older (for patients enrolled in Japan: consent from a legally acceptable representative is required for all patients who are under 20 years old). For patients in India upper age limit is 65 years old.;8. ECOG performance status 0-2.;9. Adequate organ function

as defined by the following criteria: Hepatic function:;- Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) *2.5 x upper limit of normal (ULN), or AST and ALT *5 x ULN if liver function abnormalities are due to underlying malignancy. Patients enrolled in France with ALT *3 and *5 x ULN must not have evidence of advanced fibrosis as detected by Fibrotest >0.48;- Total serum bilirubin *1.5 x ULN. Bone marrow function:;* Absolute neutrophil count (ANC) *1500/µL.;* Platelets *100,000/µL.;* Hemoglobin *9.0 g/dL. Renal function:;* Creatinine clearance (based on modified Cockcroft- Gault formula) *60 ml/min.;10. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legal representative) has been informed of all pertinent aspects of the study prior to enrollment.;11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures including completion of PRO measures.;12. Male and female patients of childbearing potential must agree to use a highly effective method of contraception throughout the study and for 90 days after the last dose of assigned treatment. Male patients randomized to Arm B must use highly effective method of contraception for a total of 180 days after last dose of chemotherapy. A patient is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

Exclusion criteria

1. Current treatment on another therapeutic clinical trial. Patients who are investigational site staff members or relatives of those site staff members, or patients who are Pfizer employess directly involved in the conduct of the trial.;2. Prior therapy directly targeting ALK.;3. Carcinomatous meningitis, or leptomeningeal disease.;4. Spinal cord compression unless treated with the patient attaining good pain control and stable or recovered neurologic function.;5. Any of the following within the 3 months prior to starting study treatment: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, or cerebrovascular accident including transient ischemic attack. Appropriate treatment with anticoagulants is permitted.;6. Ongoing congestive heart failure.;7. Ongoing cardiac dysrhythmias of NCI CTCAE Grade *2, uncontrolled atrial fibrillation of any grade, or machine-read ECG with QTc interval >470 msec.;8. Peripheral neuropathy with Grade *1 (CTCAE version 4.0).;9. 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.;10. Previous treatment with crizotinib.;11. Pregnancy or breastfeeding.;12. Use of drugs or foods that are known potent CYP3A4 inhibitors within 7 days prior to the first dose of crizotinib, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconzole, and grapefruit or grapefruit juice. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed.;13. Use of drugs that are known potent CYP3A4 inducers within 12 days prior to the first dose of crizotinib, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, , and St. John*s wort.;14. Concurrent use of drugs that are CYP3A4 substrates with narrow therapeutic indices, including but not limited to dihydroergotamine, ergotamine, pimozide, astemizole*,

cisapride*, and terfenadine* (*withdrawn from U.S. market). ;15. Prior malignancy (other than current NSCLC): patients will not be eligible if they have evidence of active malignancy (other than non-melanoma skin cancer or in situ cervical cancer, or localized and presumed cured prostate cancer) within the last 3 years.;16. Known HIV infection.;17. Other severe acute or chronic medical (including severe gastrointestinal conditions such as diarrhea or ulcer) or psychiatric conditions, or end-stage renal disease on hemodialysis. or laboratory abnormalities that would impart, 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 entry into this study.

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:	Recruitment stopped
Start date (anticipated):	11-09-2012
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Alimta
Generic name:	Pemetrexed
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin

Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Not available
Generic name:	Crizotinib

Ethics review

Approved WMO Date:	14-06-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-11-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2012
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2016
Application type:	Amendment

Review commission: METC Amsterdam UMC

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	EUCTR2010-021336-33-NL
ClinicalTrials.gov	NCT01154140
CCMO	NL34720.029.11

Study results

Results posted: 05-09-2017

Actual enrolment: 1

First publication
16-06-2015