A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Study of ARQ 197 Plus Erlotinib Versus Placebo Plus Erlotinib in Previously Treated Subjects with Locally Advanced or Metastatic, Non-Squamous, Non*Small-Cell Lung Cancer (NSCLC)

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

Summary

ID

NL-OMON36396

Source
ToetsingOnline

Brief title
ARQ197-A-U302 (008-052)

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lungcancer

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Pharmaceutical
Source(s) of monetary or material Support: Daichi Sankyo

Intervention

Keyword: Erlotinib, Lungcancer

Outcome measures

Primary outcome

The primary efficacy endpoint of the study is OS in the ITT population.

Secondary outcome

Key secondary efficacy endpoints include:

* OS in subjects with EGFR wild type (WT) NSCLC

* Progression-free survival (PFS) in the ITT population

Key safety endpoints include:

* Adverse events (AEs)

* Safety laboratory measurements and vital signs

Exploratory endpoints include:

* OS and PFS in the following subgroups:

V-Ki-ras 2 Kirsten rat sarcoma viral oncogene homolog gene (KRAS) mutant type;

MET fluorescence in situ hybridization (FISH) positive (*4); MET FISH positive

and EGFR wild type; and MET FISH positive and KRAS wild type; 1 line of prior

therapy; 2 lines of prior therapy; male subjects; female subjects;

never-smokers; current smokers; former smokers; subjects with baseline ECOG =

0; subjects with baseline ECOG = 1; Stage IIIB subjects; Stage IV subjects;

subjects age *65 years; subjects age <65 years; subjects with adenocarcinoma histology; subjects with other (non-adenocarcinoma) histology; subjects with central nervous system (CNS) metastasis; and subjects without CNS metastasis

* PFS in the EGFR wild type population

* Time to deterioration (defined as at least a 2 point decrease from baseline) on the patient-reported Pulmonary Symptom Index (PSI), a focused pulmonary symptom subscale of the Functional Assessment of Cancer Therapy-Lung (FACT-L)

* Time to deterioration in the PSI based upon alternative definitions of deterioration encompassing most of the observed range of declines on the PSI

* Cumulative distribution function of change in overall FACT-L at pre-specified time points

* Cumulative distribution function of change in the FACT-L Emotional Well Being (EWB) subscale at pre-specified time points

* Cumulative distribution function of change in PSI at pre-specified time points

* Change in patient-reported EuroQol 5-D (EQ-5D; a generic measure of standardized health status) across only different disease states

* Circulating HGF levels

* Population pharmacokinetic, pharmacogenomic, and potential pharmacodynamic parameters of ARQ 197 (analysis will be reported separately from the main study report).

Study description

Background summary

ARQ 197 is a potent and selective inhibitor of c-MET, and has demonstrated its safety and preliminary efficacy in Phase 1 clinical trials. There is evidence in a NCI-H441 human lung tumor xenograft model that, in combination with an EGFR inhibitor, the effect of ARQ 197 is greater than that with either drug alone. Furthermore, a number of Phase 1 clinical trials and a randomized, double-blinded, Phase 2 study have demonstrated safety and preliminary efficacy for ARQ 197 given as a single agent, and in combination with other agents.

Study objective

The primary objective of this study is to evaluate overall survival (OS) in the intent-to-treat (ITT) subject population defined by this protocol.
Key secondary objectives are to evaluate OS in the epidermal growth factor receptor (EGFR) wild type subpopulation; and progression-free survival (PFS) in the ITT population, and to further characterize the safety of ARQ 197 in combination with erlotinib.
Additional exploratory objectives include patient-reported outcomes (PROs), population pharmacokinetics, pharmacodynamics, pharmacogenomics, and analyses of efficacy measures in subgroups of subjects predefined in the Statistical Analysis Plan (SAP).

Study design

Randomized, stratified, double-blinded, placebo-controlled study of ARQ 197 plus erlotinib versus placebo plus erlotinib

Intervention

Subjects will receive either of 2 treatments:
ARQ 197 administered by mouth (PO), with meals, as 3 × 120 mg tablets twice daily (i.e., once in the morning and once in the evening);
plus erlotinib 150 mg administered PO once daily, at least 1 hour before or at least 2 hours after the ingestion of food, or
Placebo administered PO, with meals, as 3 tablets twice daily (ie, once in the morning and once in the evening);
plus erlotinib 150 mg administered PO once daily, at least 1 hour before or at least 2 hours after food.

Study burden and risks

The most common side effects in people treated with ARQ 197 were the following:

Frequent (10-30%)

* Nausea and vomiting
* Diarrhea, which may require medications and intravenous fluids to prevent

dehydration (loss of body water)
* Constipation
* Fatigue
* Bradycardia- Decreased heart rate: which could cause lightheadedness or fainting, data have shown that some people receiving ARQ197 showed a decrease in their resting heart rate, which stabilized throughout the course of the study treatment.
* Dizziness
* Abdominal pain
* Anorexia (loss of appetite which may lead to severe weight loss)
* Rash
* Dry skin

The side effects of erlotinib may include but are not limited to:

Common (occur in more than 20% of patients)

* Skin rash may occur in over 50% of patients
* Diarrhea (this may be treated with anti-diarrhea drugs)
* Loss of appetite
* Tiredness or fatigue
* New or worse shortness of breath
* Cough
* Nausea
* Vomiting
* Infections
* Itching
* Weight loss
* Dry skin

Potential Benefit

There may be no direct benefit to the patient from being in this study. The patient's condition may become worse or the patient may benefit from the study if he/she receives a treatment that proves to be effective. There is no guarantee that there will be any benefit to the patient. It is hoped that the results of this study will help the sponsor learn which treatments for NSCLC are safe and effective.

Contacts

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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. Male or female at least 18 years of age.;2. Histologically or cytologically confirmed surgically unresectable locally advanced or metastatic (stage IIIB/IV) non-squamous NSCLC.;3. Measurable disease and documented disease progression following last prior therapy according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, Version 1.1.;4. Have received one or two prior lines of systemic anti-cancer therapy therapy for advanced or metastatic disease, one of which must be a platinum-doublet therapy. Patients who received only adjuvant treatment will be eligible only if disease progression occurred <6 months after completion of adjuvant therapy. Prior maintenance therapy is allowed and will be considered as the same line of therapy when continued without discontinuation after initiation of a treatment regimen.;5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.;6. Resolution of any toxic effects of prior therapy (including radiotherapy) according to NCI CTCAE, Version 4.0, Grade *1 (with the exception of alopecia). Subject must have recovered from significant surgery-related complications. ;7. Demonstrate adequate bone marrow, liver, and renal functions, defined as:
* ALT, AST, and alkaline phosphatase * 2.5 × upper limit of normal (ULN) in subjects with no liver metastasis and *5.0 x ULN in subjects with liver metastasis.
* Total bilirubin * 1.5 × ULN (* 4 × ULN total and *1.5 × ULN direct bilirubin is acceptable for subjects with Gilbert*s syndrome).

* ANC *1.5 × 10e9/L.
* Platelet count *100 × 10e9/L.
* Hemoglobin *9.0 g/dL (transfusion and/or growth factor support allowed).
* Serum creatinine *1.5 × ULN or creatinine clearance * 60 mL/min.;8. Must have available archival pathology samples (10 unstained, unbaked, uncharged, paraffin-embedded slides) or tissue block suitable for analysis of KRAS, EGFR, and c-MET. (EGFR and KRAS status must be confirmed by central review prior to randomization.);9. If of child-bearing/reproductive potential (female or male), must agree to use double-barrier contraceptive measures, oral contraception, or avoidance of intercourse during the study and for 90 days after last investigational drug dose received.;10. If female and of childbearing potential, must have a negative result of a pregnancy test (serum or urine) within 72 hours prior to initiating study treatment. ;11. Must have signed and dated an IEC or IRB approved ICF (Including HIPAA authorization, if applicable) before performance of any study-specific procedures or tests. Subjects must be fully informed about their illness and the investigational nature of the study protocol (including forseeable risks and possible side effects)

Exclusion criteria

1. Prior therapy with an EGFR inhibitor and/or ARQ 197 (or other known c-MET inhibitor).;2. Receipt of any systemic anti-tumor treatment for NSCLC within 4 weeks prior to randomization.;3. Receipt of palliative radiotherapy within 2 weeks or radiotherapy for curative intent of target lesions within 4 weeks prior to randomization. (Lesions subjected to radiotherapy within 4 weeks prior to randomization may not be used as target lesions.);4. Major surgical procedure within 4 weeks prior to randomization.;5. History of cardiac disease: Congestive heart failure defined as Class II to IV per New York Heart Association classification; active coronary artery disease; previously diagnosed symptomatic bradycardia (subjects with asymptomatic bradycardia and heart rate above 50 bpm are allowed) or other cardiac arrhythmia defined as *Grade 2 according to NCI CTCAE, version 4.0, or uncontrolled hypertension; myocardial infarction that occurred within 6 months prior to study entry (myocardial infarction that occurred > 6 months prior to study entry is permitted).;6. Clinically unstable CNS metastasis (to be enrolled in the study, subjects must have confirmation of stable disease by MRI or computed tomography (CT) scan within 4 weeks of randomization and have CNS metastases well controlled by steroids, anti-epileptics or other symptom-relieving medications). ;7. Need to breastfeed a child during or within 12 weeks of completing the study.;8. Significant gastrointestinal disorder that, in the opinion of the investigator, could interfere with absorption of ARQ 197 and/or erlotinib (eg, Crohn*s disease, small or large bowel resection, malabsorption syndrome). ;9. Inability or unwillingness to swallow the complete doses of ARQ 197 or erlotinib.;10. Any known contraindication to treatment with, including hypersensitivity to, ARQ 197 or erlotinib.;11. History of malignancy other than NSCLC within the 5 years prior to randomization, with the exceptions of adequately treated intraepithelial carcinoma of the cervix uteri; prostate carcinoma with a prostate-specific antigen value <0.2 ng/mL; or basal or squamous-cell carcinoma of the skin.;12. Known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV).;13. Any other significant co-morbid condition that, in opinion of the investigator, would impair study participation or cooperation.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2011
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ARQ197
Generic name:	NA

Ethics review

Approved WMO Date:	24-02-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	16-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2012
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	EUCTR2010-022365-10-NL
ClinicalTrials.gov	NCT01244191
CCMO	NL35273.018.11