A randomized, Phase III, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Onartuzumab (MetMAb) in Combination with Tarceva® (erlotinib) in Patients with Met Diagnostic-Positive Non-Small Cell Lung Cancer (NSCLC) Who Have Received Standard Chemotherapy for Advanced or Metastatic Disease

Published: 21-02-2012
Last updated: 26-04-2024

Primary Objective To determine whether the combination of Onartuzumab + * erlotinib is superior (in terms of OS) to placebo * erlotinib after standard platinum-based chemotherapy in patients with Met diagnostic*positive non*small cell lung cancer (...

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

Summary

ID

NL-OMON39593

Source
ToetsingOnline

Brief title
OAM4971g

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Incurable lung cancer, Non-Small Cellular Long Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Registration Ltd.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Met Diagnostic-positive Non-Small Cell Lung Cancer (NSCLC), MetMAb, Phase III, Tarceva® (erlotinib)

Outcome measures

Primary outcome

Primary Efficacy Endpoint: Overall Survival

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. The data cutoff is planned for the final analysis when 364 death events have occurred.

The treatment comparison of OS will be based on a stratified log-rank test at the 0.025 level of significance (one-sided) for all ITT patients. The stratification factors are Met expression (2 * vs. 3 *), prior lines of therapy (1 vs. 2), histology (nonsquamous vs. squamous), and EGFR activating mutation status (yes vs. no) and will be based on data collected on eCRFs. Results from an unstratified log rank test will also be presented. Kaplan*Meier methodology will be used to estimate median OS for each treatment arm, and the Kaplan*Meier

curve will be constructed to provide a visual description of the difference between the treatment arms. Estimates of the treatment effect will be expressed as hazard ratios (HRs) with use of a stratified Cox model, including 95% confidence intervals (CIs).

Secondary outcome

Secondary Efficacy Endpoints

* If the primary endpoint of OS is statistically significant at a one-sided 2.5% significance level, the secondary endpoints of PFS and ORR will be tested in order (PFS followed by ORR), each at a one-sided 2.5% significance level.

PFS

ORR

PROs

* Exploratory Efficacy Outcome Measures

DCR based on tumor responses (based on RECIST v1.1)

DOR (based on RECIST v1.1)

Changes in ECG measures from baseline, including QT/QTc intervals, at Cycle 4 and as clinically indicated; C-QTc assessment as applicable.

Study description

Background summary

EGFR inhibitors are increasingly used as therapy for human cancers, but development of resistance presents a challenge. Recently, genetic amplification and over-expression of Met have been implicated in driving resistance to EGFR inhibitors, both in NSCLC cell lines and in patients (Engelman et al. 2007). Met or EGFR signaling reinforces activation of the other pathway. These data suggest that Met and EGFR cooperate to drive tumor growth and survival and

therefore support a strong rationale for combining Met and EGFR inhibitors in the clinic.

The Phase I study evaluating Onartuzumab in advanced solid malignancies (Study OAM4224g) showed that the drug was tolerable up to 30 mg/kg, with onlya single DLT of Grade 3 pyrexia occurring at 4 mg/kg (Moss et al. 2010).

The Phase II randomized trial of erlotinib ± Onartuzumab (IV 15 mg/kg, Q3W) in previously treated patients with advanced NSCLC (Study OAM4558g) showed that patients whose tumors were Met diagnostic positive had an improvement in PFS (stratified HR = 0.53; 95% confidence interval [CI], 0.28, 0.99) and in OS (stratified HR = 0.37; 95% CI, 0.19, 0.72), while patients who were Met diagnostic negative showed a worse outcome in PFS (stratified HR = 1.82; 95% CI, 0.99, 3.32) and in OS (stratified HR = 1.78; 95% CI, 0.79, 3.99) (Spigel et al. 2011) The toxicity profile for erlotinib ± Onartuzumab treatment was similar to that for erlotinib alone, with the exception of peripheral edema in patients who received the combination treatment.

These results suggest that Onartuzumab should be further evaluated as second- or third-line treatment in Met diagnostic*positive NSCLC.

Study objective

Primary Objective
To determine whether the combination of Onartuzumab + * erlotinib is superior (in terms of OS) to placebo * erlotinib after standard platinum-based chemotherapy in patients with Met diagnostic*positive non*small cell lung cancer (NSCLC)

Secondary Objectives
* To evaluate and compare the efficacy in terms of progression-free survival (PFS) and (objective response rate) ORR between the two treatment groups
* To evaluate and compare the safety and tolerability of Onartuzumab +* erlotinib versus placebo * erlotinib in patients with Met diagnostic*positive NSCLC
* To evaluate the impact of Onartuzumab on patient reported outcome (PRO) measures of quality of life
* To evaluate the pharmacokinetics of Onartuzumab
* To evaluate serum levels and incidence of anti-therapeutic antibodies (ATAs) against Onartuzumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, safety, and efficacy

Study design

This is a randomized, Phase III, multicenter, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of Onartuzumab in

combination with erlotinib as compared with treatment with erlotinib alone in patients with incurable NSCLC identified to be Met diagnostic positive.
Tumor specimens from patients meeting eligibility criteria will be prospectively tested for Met receptor expression by the Ventana anti-Total c MET (SP44) rabbit monoclonal antibody IHC assay and for EGFR activating mutation status by the RMS cobas* EGFR Mutation Test. Only patients with Met diagnostic*positive tumors will be enrolled. Eligible patients will be stratified by Met expression (clinical score of 2 * vs. 3 *), number of prior lines of therapy (1 vs. 2), histology (nonsquamous vs. squamous), and epidermal growth factor receptor (EGFR)*activating mutation status (yes vs. no).
Patients will be randomized in a 1:1 ratio to receive either Onartuzumab + * erlotinib or placebo * erlotinib on a 21-day cycle. Approximately 490 patients are planned to be enrolled.
Treatment will continue until disease progression, unacceptable toxicity, patient or physician decision to discontinue, or death. Assessment for tumor response will occur every 6 weeks with use of Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Tumor response data collection will continue if the patient ends treatment prior to disease progression. Follow up data capture, including subsequent anti-cancer therapies, will continue for each patient until death or discontinuation from the study.
An independent Data Monitoring Committee (IDMC) will monitor safety data. One interim analysis of efficacy and futility is planned for when approximately 67% of the total overall survival (OS) events have been observed.

Intervention

- Arm A: erlotinib and Onartuzumab
- Arm B: erlotinib and placebo (an inactive substance)

On Day 1 of each cycle, the subject will receive either Onartuzumab or placebo (depending on the treatment arm to which you are assigned) administered intravenously (into the vein). For the first cycle, the intravenous dose of study drug will occur over about 60 minutes; subsequent doses may be decreased to about 30 minutes, depending on how the subject tolerates the first dose.
The dose of study drug will be based on weight at screening and will remain the same throughout the study.
On Day 1, the subject will be given a sufficient amount of erlotinib tablets for the entire cycle of 21 days, with instructions on how to take the drug at home. The subject will take a 150 mg tablet by mouth with approximately 200 mL (6*8 ounces) of water on an empty stomach every day (either 1 hour before or 2 hours after eating) for the entire time he/she is participating in the study.

Study burden and risks

Please refer to appendix A of the protocol for an overview of all study visits and procedures.

Summary of procedures:

7x Vital signs
7x Physical examination
7x Pregnancy Test
8x Urine testing
6x Administration of study drug
3x ECG
9x Tumor assessment: CT- / MRI-scan
9x Additional blood samples
9x Quality of Questionnaires (3)

This study can have the following side-effects:

Onartuzumab side effects
The initial experience with Onartuzumab in humans was evaluated in a clinical research study that tested the safety of increasing Onartuzumab doses in patients. The most common side effects reported in at least 10% of the patients receiving Onartuzumab were fatique, peripheral edema (swelling), nausea, low blood albumin (a protein). The less common side effects reported in less than 10% of the patients receiving Onartuzumab were vomiting, loss of appetite, muscle spasms, abdominal pain, weight gain, fever, low blood sodium, AST (liver function test) high.
Results from a clinical research study evaluating the activity of Onartuzumab in combination with erlotinib in patients with NSCLC showed that this combination resulted in a higher rate (more than 10% difference) of edema compared with erlotinib alone. Results from this study were also analyzed with respect to the expression levels of the Met protein (i.e., levels of the Met protein that each patient*s cells are producing). In patients whose tumors had higher levels of the Met expression (as in this study), the addition of MetMAb resulted in an increase (* 10% difference) in abdominal pain and edema.
The most common side effects reported in * 10% of the patients receiving Onartuzumab in combination with erlotinib wererash, infections diarrhea, neasea, peripheral edema (swelling), loss of appetite, shortness of breath, acne-like dermatitis, cough, fever, anemia (low red blood cell count), insomnia (trouble sleeping), weakness, dry skin and back pain.

Erlotinib Side Effects
Side effects that have been reported by at least 10% of patients receiving erlotinib include skin rash, diarrhea, fatigue, loss of appetite, shortness of breath, cough, nausea, infection, vomiting. Mouth sores, itchy skin, dry skin, eye irritation, dry eyes and stomach pain.

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

* ECOG performance status of 0*1
* Stage IIIb/IV NSCLC
* Tumor sample to be centrally tested for Met and EGFR (tumor results must be Met diagnostic-positive)
* Prior treatment with at least one platinum-based line of treatment for locally advanced, unresectable / inoperable disease or metastatic disease, and no more than one additional line of chemotherapy treatment

Exclusion criteria

* More than 30 days with an EGFR inhibitor (such as gefitinib, erlotinib, cetuximab)

* Pleural effusion, pericardial fluid, or ascites requiring drainage every other week or more frequently
* Brain metastasis or spinal cord compression unless treated and stable
* Another malignancy in the past 5 years except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other malignancies with an expected curative outcome
* Life expectancy less than 12 weeks
* Abnormal granulocytes, platelets, hemoglobin
* Abnormal serum AST (SGOT), ALT (SGPT), alkaline phosphatase (ALP), bilirubin, albumin, calcium, creatinine
* Significant history of cardiac disease
* Serious active infection or other serious medical conditions
* Inflammatory eye changes
* Clinically significant gastrointestinal abnormalities
* Unable to take oral medication, need for intravenous feeding, poor absorption, or active peptic ulcer disease
* Symptomatic hypercalcemia requiring bisphosphonate therapy
* Patients with uncontrolled diabetes mellitus, as evidenced by fasting serum glucose level > 200 mg/dL
* Recent major surgery

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:	Recruitment stopped
Start date (anticipated):	26-10-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Onartuzumab / MetMAb
Generic name:	Onartuzumab
Product type:	Medicine
Brand name:	Tarceva
Generic name:	Erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-02-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-06-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-08-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-08-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-10-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-12-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-01-2015
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
EudraCT	EUCTR2011-002224-40-NL
ClinicalTrials.gov	NCT01456325
CCMO	NL39298.068.12