A Multicenter, Open Label, Randomized Study of AMG 951 in Subjects with Previously Untreated Stage IIIb/IV Non-Small Cell Lung Cancer (NSCLC) Treated with Chemotherapy with or without Bevacizumab

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Objectives:Phase 1b: To determine the maximum tolerated dose (MTD) (up to 8mg/kg/day) through safety and tolerability of multiple doses of AMG 951 administered by intravenous (IV) infusion to subjects with NSCLC in combination with chemotherapy and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON31650

Source
ToetsingOnline

Brief title
not applicable

Condition

- Respiratory tract neoplasms

Synonym
lungcancer, Non Small Cell Lungcancer

Research involving

Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Amgen BV Breda

Intervention

Keyword: AMG951, Bevacizumab, Chemotherapy, Non Small Lung Cancer stage IIIB/IV

Outcome measures

Primary outcome

End point: Phase 1b:

Primary Endpoint:

· Incidence of dose-limiting toxicities (DLTs)

· Incidence and severity of adverse events

End point: Phase 2:

Primary Endpoint:

· Objective response rate (complete or partial response)

Secondary outcome

Phase II:

Secondary Efficacy Endpoints:

· Overall survival

· Progression free survival

· Time to response

· Duration of response

· Time to progression

Study description

Background summary

In this study, the study medication AMG 951 is evaluated for the treatment of patients with non-small cell lung carcinoma. AMG 951 is considered experimental. Carboplatin and paclitaxel are chemotherapy medications that have been approved as a treatment regimen for non-small cell lung cancer by Regulatory Agencies. Bevacizumab (Avastin) is not approved for non-small cell lung cancer treatment. Bevacizumab has been approved for use in colorectal cancer.
AMG 951 will be administered in this study along with the carboplatin and paclitaxel chemotherapy regimen and bevacizumab.
AMG 951 is produced using recombinant DNA technology. AMG 951 binds to specific places on cancer cells and causes the cells to die in laboratory studies. This experimental drug has prevented or slowed the growth of several different types of human cancer cells grown in animals. Up to now, in the first study of AMG 951 in humans, doses of 15 mg/kg, 8 mg/kg and 4 mg/kg (similar to the doses to be given in this study) have been given safely with no significant side effects in 50 people.
Approximately 200 subjects will participate in the research study.
Approximately twenty centers in Europe will be involved. The study may also be expanded to other regions of the world as necessary.

Study objective

Objectives:
Phase 1b: To determine the maximum tolerated dose (MTD) (up to 8mg/kg/day) through safety and tolerability of multiple doses of AMG 951 administered by intravenous (IV) infusion to subjects with NSCLC in combination with chemotherapy and bevacizumab

Phase 2: To evaluate the objective response rate by modified RECIST for AMG 951 at varying dose schedules in combination with carboplatin / paclitaxel ± bevacizumab for subjects with NSCLC.

Study design

Study design:
This is a phase 1b/2 multicenter, open label, randomised study of AMG 951 in

subjects with previously untreated stage IIIb/IV NSCLC treated with chemotherapy with or without bevacizumab.

For the phase 1b portion of the study, six subjects per group will receive Paclitaxel (200 mg / m2 over 3 hours (± 10 minutes)), carboplatin (AUC=6.0 mg/mL.min IV over 15-30 minutes) and bevacizumab (15 mg/kg IV over 90 minutes (+ 10 minutes)) on day 1. This will be followed by AMG 951 at the assigned dose (continuous IV infusion over 60 minutes ± 10 minutes). AMG 951 will be given once daily on days 1-5. Up to 6 cycles of treatment will be administered.
Six subjects will be enrolled into cohort A1 to receive chemotherapy, bevacizumab and AMG 951 at 4 mg/kg/day. Following review of the DLT data, a further six subjects will be enrolled into either cohort A2 (chemotherapy, bevacizumab and AMG 951 at 8 mg/kg/day) or cohort A3 (chemotherapy, bevacizumab and AMG 951 at 1.5 mg/kg/day). Only subjects eligible to receive bevacizumab will be enrolled into the phase 1b study. Subjects with squamous NSCLC and/or CNS metastases will not be enrolled into the phase 1b study.

For the phase 2 portion of the study, subjects will be assigned to a set of treatment groups depending on their eligibility to receive bevacizumab. Subjects with squamous NSCLC and/or CNS metastases will not be eligible to receive bevacizumab and will be assigned to either cohort A or B. Subjects who are eligible to receive bevacizumab will be assigned to cohort C, D or E. Cohorts are defined as follows:

Subjects with squamous NSCLC or CNS mets:
Cohort A: Chemotherapy alone
Cohort B: Chemotherapy plus 8 mg/kg AMG 951 for 5 days

Subjects without squamous NSCLC and without CNS mets:
Cohort C: Chemotherapy and bevacizumab
Cohort D: Chemotherapy, bevacizumab plus 8 mg/kg AMG 951 for 5 days
Cohort E: Chemotherapy, bevacizumab plus 8 mg/kg AMG 951 for 2 days

Intervention

Phase 1b:
Six subjects will be enrolled into cohort A1 to receive chemotherapy, bevacizumab and AMG 951 at 4 mg/kg/day. Following review of the DLT data, a further six subjects will be enrolled into either cohort A2 (chemotherapy, bevacizumab and AMG 951 at 8 mg/kg/day) or cohort A3 (chemotherapy, bevacizumab and AMG 951 at 1.5 mg/kg/day). Only subjects eligible to receive bevacizumab will be enrolled into the phase 1b study. Subjects with squamous NSCLC and/or CNS metastases will not be enrolled into the phase 1b study.

Phase II:
Subjects with squamous NSCLC or CNS mets:

Cohort A: Chemotherapy alone
Cohort B: Chemotherapy plus 8 mg/kg AMG 951 for 5 days

Subjects without squamous NSCLC and without CNS mets:
Cohort C: Chemotherapy and bevacizumab
Cohort D: Chemotherapy, bevacizumab plus 8 mg/kg AMG 951 for 5 days
Cohort E: Chemotherapy, bevacizumab plus 8 mg/kg AMG 951 for 2 days

Study burden and risks

Burden for the patients:

Regular visits to the hospital to undergo the procedures as defined in Appendix A: medical and medication history, physical exam, vital signs, brain CT/MRI scan, ECG, hematology, chemistry, AMG 951 and antibody levels. Adverse events and concomitant medications will be recorded throughout study participation.

Risk:
In five randomised clinical trials, the incidence of arterial thromboembolic events including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.
A history of arterial thromboembolic events or age over 65 years was associated with an increased risk of developing arterial thromboembolic events during therapy. Caution should be taken when treating these patients with bevacizumab. Therapy should be permanently discontinued in patients who develop arterial thromboembolic events.
Prior anthracycline exposure and/or prior radiation to the chest wall may be possible risk factors for the development of Congestive Heart Failure. Caution should be exercised before initiating Bevacizumab therapy in patients with these risk factors.
The highest dose of bevacizumab tested in humans (20 mg/kg of body weight, intravenous) was associated with severe migraine in several patients. Overdose with this product have not been reported.

Contacts

Public
Amgen

Minervum 7061
4817 ZK Breda
Nederland

Scientific
Amgen

Minervum 7061
4817 ZK Breda
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

· Histologically or cytologically confirmed Non-Small Cell Lung Cancer (NSCLC).
· Subjects must have advanced NSCLC stage IIIb or Stage IV disease.
. Planning to receive at least 6 cycles of therapy
· ECOG performance status of 0 or 1
· Life expectancy greater than 3 months
· ³18 years old
· INR £ 1.2 and PTT is no greater than ULN within 1 week prior to enrollment

Exclusion criteria

· Prior malignancy other than NSCLC (except in situ basal cell carcinoma or in situ cervical cancer), unless have been treated with curative intent with no evidence of disease for ³ 3 years
· Myocardial infarction, or unstable or uncontrolled disease or condition related to or impacting cardiac function within 1 year of enrollment
· Uncontrolled hypertension
· History of arterial thrombosis, pulmonary embolus within 1 year of

enrollment
· Recent major surgical procedure within 28 days of enrollment
· Subjects must not have serious non-healing wound ulcer, or bone fracture within 21 days prior to enrollment
. Prior chemotherapy

Study design

Design

Study phase:	2
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):	01-06-2006
Enrollment:	19
Type:	Anticipated

Medical products/devices used

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

Ethics review

Approved WMO

Date:	22-05-2006

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2008
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	EUCTR2005-005484-28-NL
CCMO	NL11656.029.06