An open-label, randomized, Phase IIIb trial evaluating the efficacy and safety of standard of care +/- continuous bevacizumab treatment beyond progression of disease (PD) in patients with advanced non-squamous non-small cell lung cancer (NSCLC) after first (1st)-line treatment with bevacizumab plus a platinum doublet-containing chemotherapy

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The main aim of this study is to find out if the continuation of bevacizumab, in addition to standard 2nd & 3rd -line treatment, can help patients with NSCLC that has progressed to live longer. The study also aims to find out if continued…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON39879

Source
ToetsingOnline

Brief title
AvaALL

Condition

- Miscellaneous and site unspecified neoplasms benign
- Respiratory tract neoplasms

Synonym
Lungcancer, non-small lung cancer, Non-squamous

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Roche Nederland B.V.

Intervention

Keyword: bevacizumab, continuous treatment, NSCLC

Outcome measures

Primary outcome

2. OBJECTIVES

2.1 Primary Objective

* To assess the efficacy of continuous bevacizumab treatment beyond PD1 as measured by OS.

Secondary outcome

2.2 Secondary Objectives

* To assess the efficacy as measured by rate of 6-, 12-, and 18-month OS as measured from randomization at PD1.

* To assess the efficacy as measured by PFS and TTP from randomization at PD1 to PD2 (PFS2, TTP2), and to PD3

* To assess the efficacy as measured by RR, disease control rates, and duration

of response at PD2 and PD3.

* To assess the efficacy in the subgroup of adenocarcinoma patients.

* To assess the safety of bevacizumab treatment across multiple lines of

treatment.

2.3 Exploratory Objectives

* To assess QoL through multiple lines of treatment.

* To compare the efficacy between Asian and non-Asian patients.

Study description

Background summary

Recurrent or metastatic NSCLC can be improved by some drug treatment. There remains, however, a great need for additional treatments that will maintain the health of patients with recurrent or metastatic NSCLC for longer periods of time.
Bevacizumab is often combined with two chemotherapy drugs for the initial treatment of NSCLC. At present, bevacizumab and both chemotherapy drugs are ceased if and when NSCLC progresses (i.e. the cancer regrowth at the same location or a cancer is found at a new location in the body (metastasis). Many patients will then be offered new treatment with different anti-cancer drugs (standard 2nd -line treatment) in order to reduce the growth of the cancer cells again. Upon subsequent regrowth some patients are again offered different anticancer drugs (3rd line treatment).

Study objective

The main aim of this study is to find out if the continuation of bevacizumab, in addition to standard 2nd & 3rd -line treatment, can help patients with NSCLC that has progressed to live longer. The study also aims to find out if continued bevacizumab will help patients live longer free of tumor re-growing or spreading and if it is generally safe to use bevacizumab in combination with standard treatment for NSCLC that has progressed.

Study design

3. TRIAL DESIGN

3.1 Overview of Trial Design
This is a two-arm, open-label, randomized, multicenter, phase IIIb trial (see Figure 1).
Patients randomized to Arm A will receive bevacizumab 7.5 mg/kg i.v. or 15 mg/kg i.v. on Day 1 every 21 days (+/- 3 days) (to coincide with SOC treatment) from Cycle 1 until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first). The dose of bevacizumab should be the same dose that was administered during 1st-line and maintenance treatment.
Patients randomized to Arm B will not receive bevacizumab
All patients (Arm A and Arm B) will receive one of the following drugs as 2nd-line SOC treatment until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first):
* Erlotinib 150 mg daily taken on an empty stomach at least one hour before or two hours after the ingestion of food
or
* Docetaxel 75 mg/m2 on Day 1 every 21 days (+/- 3 days).
or
* Pemetrexed 500 mg/m2 i.v. over 10 minutes on Day 1 every 21 days (+/- 3 days).
The 2nd-line SOC agent will be selected by the investigator prior to randomization.
Following PD2/3, 3rd and 4th-line SOC treatment, respectively, will be chosen by the investigator according to local practice (Section 6.4).
SOC treatment can be altered or ceased or changed for PD or unacceptable toxicity. If SOC treatment is ceased permanently, bevacizumab treatment should continue provided there is no unacceptable toxicity related to bevacizumab or withdrawal of consent (see Section 4.5 for other reasons of premature discontinuation).

Arm A: Patients will receive bevacizumab 7.5 mg/kg i.v. or 15 mg/kg i.v. on Day 1 every 21 days (+/- 3 days) in combination with SOC treatment from Cycle 1 until the occurrence of an unacceptable toxicity or withdrawal of consent (whichever occurs first). The dose of bevacizumab should be the same dose that was administered during 1st-line and maintenance treatment.
Arm B: Patients will receive SOC treatment without bevacizumab until unacceptable toxicity or withdrawal of consent (whichever occurs first).
SOC treatment can be changed for toxicity or progression of disease (PD).

Intervention

Standard treatment with or without bevacizumab (until progression).

Study burden and risks

Burden and risk:

The most important adverse events of bevacizumab that occur at more than 10% of the patients are:
* High blood pressure (hypertension)
* Numbness or loss of feeling in the fingers or toes (peripheral sensory neuropathy
* Low numbers of white blood cells (neutropenia, leucopenia) and potentially associated with fever (febrile neutropenia)
* Low numbers of platelets (thrombocytopenia)
* Shortness of breath (dyspnea)
* Diarrhea
* Bleeding from the rectum (rectal hemorrhage)
* Nausea and vomiting
* Pain, including headache and joints pain (arthralgia)
* Alteration in speech (dysarthria)
* Constipation
* Mucosal inflammation or inflammation of the mouth (stomatitis)
* Protein in urine
* Mucocutaneous bleeding, including nose bleed (epistaxis)
* Lack of energy, weakness (asthenia, fatigue)
* Loss of appetite (anorexia)
* Fever (pyrexia)
* Runny nose (rhinitis)
* Dry skin, flaking and inflammation of the skin (exfoliative dermatitis)
* Change in skin color (skin discoloration)
* Change in the sense of taste (dysgeusia)
* Eye disorder, tearing (lacrimation increased)

Bevacizumab may also cause changes in laboratory tests carried out by your doctor. These include: decreased blood
potassium and sodium; increased blood sugar; altered coagulation values.

Some adverse events are more common in elderly patients that in younger patients. This is the case with arterial thromboembolic events, that can cause a stroke or heart attack. Elderly patients also have an increased change of leucopenia and thrombocytopenia.

Some adverse events are seen rarely or very rarely. A list of these adverse events can be found in the patient information sheet. It is possible that unknown adverse events occur.

Benefit:
The aim of this study is to find out if the continuation of bevacizumab, in addition to standard 2nd & 3rd -line treatment, can help patients with NSCLC that has progressed to live longer.

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

- Adult patients, age >/<=18 years;- Histologically or cytologically confirmed non-squamous non-small cell lung cancer (NSCLC) ;- Documented progression of disease (locally recurrent or metastatic) per investigator assessment following first-line treatment 4-6 cycles of Avastin plus a platinum doublet-containing chemotherapy regimen and a minimum of 2 cycles of Avastin (monotherapy) maintenance treatment prior to first progression of disease;- No treatment interruption of Avastin treatment greater than 2 consecutive cycles (42 days) between the start of first-line treatment to start of Cycle 1 of second line treatment;- Randomization within 4 weeks of progression of disease;- At least one unidimensionally measurable lesion meeting RECIST criteria;- Eastern Cooperative Oncology Group (ECOG) performance status 0-2

Exclusion criteria

- Mixed, non-small cell and small cell tumors or mixed adenosquamous carcinomas with a predominant squamous component;- History of pulmonary hemorrhage/hemoptysis >/=grade 2 within 3 months of randomization;- Major cardiac disease

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):	04-11-2011
Enrollment:	25
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	11-02-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	22-07-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	30-08-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	16-09-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	14-10-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	06-01-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	16-01-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	12-03-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-03-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-05-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-07-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-02-2013
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:	13-01-2014

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-10-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-01-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-03-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	31-12-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-01-2016
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	EUCTR2010-022645-14-NL
Other	EUDRACT: 2010-022645-14
CCMO	NL35187.068.11