A randomized phase II study of paclitaxel-carboplatin-bevacizumab with or without nitroglycerin patches in patients with stage IV non-squamous-non-small cell lung cancer: NVALT12

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The addition of NTG patches to bevacizumab containing chemotherapy (experimental arm) improves PFS in patients with stage IV non-squamous NSCLC, compared to bevacizumab containing chemotherapy without NTG (control arm)Secondary Objectives: Objective...

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

Summary

ID

NL-OMON36516

Source
ToetsingOnline

Brief title
NVALT12

Condition

- Respiratory tract neoplasms

Synonym
non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Stichting NVALT studies
Source(s) of monetary or material Support: NVALT

Intervention

Keyword: bevacizumab, metastatic, nitroglycerin, non-small cell lung cancer

Outcome measures

Primary outcome

Progression free survival.

Secondary outcome

Objective response rate (ORR) and disease control rate (DCR), Duration of

response, OS, Safety.

Study description

Background summary

Standard treatment for non-small cell lung cancer (NSCLC) consists of platinum-containing chemotherapy. It has been shown that the addition of bevacizumab to standard chemotherapy improves progression-free survival (PFS) and overall survival (OS) in patients with non-squamous NSCLC. There is a need for improved PFS and OS and response rates to chemotherapy are only 25-35%.
Tumor hypoxia is a common phenomenon in lung cancer; it is a known poor prognostic marker, related to treatment resistance. Hypoxia Inducible Factor (HIF) -1* is the major factor regulating the response to hypoxia.
HIF directly activates vascular endothelial growth factor (VEGF) and VEGF-receptor. Bevacizumab interacts with this pathway by blocking VEGF.
Pre-clinical studies have shown that nitric oxide (NO) donating drugs may decrease hypoxia related drug resistance. Nitrogycerine (NTG) is a NO donating drug. NTG increases tumor blood flow and thereby augments antitumor drug delivery to the tumor and inhibits HIF-1*.
Interestingly, it has recently been shown in mouse models that the addition of HIF-1* inhibitors to bevacizumab significantly inhibits tumor growth by inducing apoptosis.
A randomized phase II has shown an increase in the response rate from 42% to 72%, when NTG patches (25 mg/day, day *2 to +3) were added to

vinorelbine/cisplatin in patients with advanced NSCLC. In addition, the time to progression increased from 185 to 327 days.
The hypothesis of the present study is that adding NTG transdermal patches to bevacizumab containing chemotherapy improves progression free survival (PFS), response rate (RR) and overall survival (OS) in patients with metastatic non-squamous NSCLC. Because of the expected high rate of headache, the daily dose of NTG has been reduced to 15 mg/24 h.

Study objective

The addition of NTG patches to bevacizumab containing chemotherapy (experimental arm) improves PFS in patients with stage IV non-squamous NSCLC, compared to bevacizumab containing chemotherapy without NTG (control arm)
Secondary Objectives: Objective response rate (ORR) and disease control rate (DCR), Duration of response, OS, Safety.
Exploratory Objectives: Prediction of early response and decrease of hypoxia by [18F]FDG-PET-scan, Investigating the effect on tumor hypoxia by [18F]HX4 or [18F]FAZA scans (selected centers), Evaluation of response by blood- and tumor biomarkers.

Study design

Multicenter randomized open phase II parallel group study.
Patient will be randomly allocated to either:
1. Standard treatment: paclitaxel 200 mg/m2 d1 * carboplatin AUC 6 d1 - bevacizumab 15 mg/kg d1. Cycles every 3 weeks. Paclitaxel and carboplatin 4 cycles. Bevacizumab till progression.
2. Experimental treatment: paclitaxel 200 mg/m2 d1 * carboplatin AUC 6 d1 - bevacizumab 15 mg/kg d1. Cycles every 3 weeks. Paclitaxel and carboplatin 4 cycles. Bevacizumab till progression. Plus nitroglycerin transdermal patches 15 mg per 24h from day -3 till +2 of First combination cycle till the last bevacizumab monotherapy cycle.
Study duration: till disease progression. Thereafter follow-up for survival.
222 patients.

Intervention

Treatment with standard treatment +/- nitroglycerin.

Study burden and risks

Risk: Adverse events of nitroglycerin.
Burden: The study follows the standard treatment for medication (except NTG patches), hospital visits, safety blood tests and imaging (except PET scans).
Extra tests:
Blood tests biomarkers 4x 20-40 ml/visit.

In centres with FDG PET scans as standard diagnostic tool, this FDG PET scan will be repeated after the 1st cycle. De hypoxia PET scan will only be conducted in selected centres.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Histologically/cytologically proven stage IV non-squamous NSCLC (according to IASLC staging 7.0)
* No prior chemotherapy or therapy with systemic anti-tumor therapy (e.g., monoclonal antibody therapy) or prior exposure to agents directed at the HER axis (e.g. EGFR TK inhibitors, Herceptin). Prior surgery and/or localized palliative irradiation is permitted provided that the irradiated lesion is not the only measurable lesion. Prior adjuvant chemotherapy > 1 year ago and prior treatment with an EGFR-TKI for patients with an

activating EGFR mutation is allowed.
* Age * 18 years.
* ECOG Performance Status of 0 * 2.
* Life expectancy of at least 12 weeks.
* Subjects with at least one uni-dimensional(for RECIST) measurable lesion.
* Adequate bone marrow, liver and renal function (see protocol for details).
* Adequate non-hormonal contraception for females of childbearing potential during the study and in the 6 months thereafter.
* Adequate contraception for male participants (or their partners) during the study and in the 6 months thereafter.

Exclusion criteria

* Clinically significant (i.e. active) cardiovascular disease: congestive heart failure >NYHA class 2; CVA or myocardial infarction < 6 months prior to study entry; uncontrolled hypertension (blood pressure systolic > 150 mmHg and/or diastolic > 100 mmHg).
* Symptomatic hypotension.
* History of hemoptysis at least grade 2 (bright red blood of at least 2,5 ml in the last 3 months)
* Evidence of tumor invading major blood vessels on imaging (i.e. superior vena cava or pulmonary artery).
* History of HIV infection or chronic hepatitis B or C.
* Active clinically serious infection
* Symptomatic metastatic brain or meningeal tumors. Patients with brain metastasis may be included the patient is treated with brain radiotherapy and asymptomatic.
* History of organ allograft.
* Patients with evidence or history of bleeding diathesis.
* Non-healing wound or ulcer.
* History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months of enrolment
* Anticancer chemotherapy or immunotherapy during the study or within 4 weeks of study entry
* Radiotherapy within 4 weeks of start of study drug. Palliative radiotherapy for bone lesions is allowed > 14 days of start of chemotherapy. Major surgery within 4 weeks of start of study.
* Use of vasodilators (including 5-fosfodiesterase inhibitors, calcium antagonists or nitrates)
* Autologous bone marrow transplant or stem cell rescue within 4 months of study
* Investigational drug therapy outside of this trial during or within 4 weeks of study entry
* Pregnancy or lactation.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-01-2011
Enrollment:	222
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nitroglycerin patch
Generic name:	nitroglycerin patch
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-08-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-11-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-05-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	16-06-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	29-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
Other	clinicaltrials.gov NCT01171170

Register	ID
EudraCT	EUCTR2010-022104-50-NL
CCMO	NL33442.042.10