A Phase III Randomized, Double-blind, Placebo Controlled Trial Comparing the Efficacy of Gemcitabine, Cisplatin and Sorafenib to Gemcitabine, Cisplatin and Placebo in First-Line Treatment of Patients with Stage IIIb with effusion and stage IV Non-Small Cell Lung Cancer (NSCLC)

Published: 16-11-2006
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON31507

Source
ToetsingOnline

Brief title
NvT

Condition

- Respiratory tract neoplasms

Synonym
lung cancer, non-small cell lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cisplatin, gemcitabine, NSCLC, sorafenib

Outcome measures

Primary outcome

The primary efficacy objective is to compare progression-free survival and

overall-survival of sorafenib in combination with gemcitabine and cisplatin

versus placebo in combination with gemcitabine and cisplatin.

Statistical considerations including sample size determination are outlined in

Section 6 of the protocol.

Secondary outcome

Safety and patient reported outcome (PRO)

Study description

Background summary

Lung cancer is the leading cause of cancer death in North America and worldwide and non-small cell lung cancer (NSCLC) is responsible for 75%-80% of all lung malignancies. More than 60% of patients present with metastatic (Stage IV) disease (1, 2). In addition, most patients presenting with earlier-stage disease eventually develop metastases.
The only potentially curative treatment for patients with NSCLC is surgical resection, but surgery is an option for only a small fraction of patients with

localized disease. Fewer than 30% of patients are suitable candidates for pulmonary resection because of regional or distant spread at the time of diagnosis, poor pulmonary function or both. For patients presenting with unresectable advanced disease, the primary goal of therapy is palliative. Untreated metastatic NSCLC has a poor prognosis with a one year survival of approximately 10% (3).
The efficacy of angiogenesis inhibitors in the treatment of NSCLC has been demonstrated in a pivotal Phase III study, whereby bevacizumab (a recombinant, humanized anti-VEGF (vascular endothelial growth factor) monoclonal antibody) in combination with carboplatin and paclitaxel provides a statistically significant survival advantage with tolerable toxicity (7). The evaluation of bevacizumab and other platinum-based regimens, e.g. (exempli gratia, for example) carboplatin/gemcitabine and oxaliplatin/gemcitabin is ongoing (8, 9)

Study objective

The objective of this phase III study is to compare the efficacy of sorafenib in combination with gemcitabine and cisplatin versus placebo with gemcitabine and cisplatin for first-line treatment of patients with stage IIIB (with effusion) or Stage IV NSCLC of non squamous cell carcinoma subtype.

Study design

This is a randomized, double blind, placebo controlled, multicenter, Phase III study designed to compare the efficacy of sorafenib in combination with gemcitabine and cisplatin versus placebo in combination with gemcitabine and cisplatin for patients with NSCLC (Stage IV or Stage IIIB with effusion). Approximately 990 patients will receive up to 6 cycles of gemcitabine and cisplatin in combination with either sorafenib or placebo in a blinded fashion.
It is estimated that enrollment will take approximately 17 months with an enrollment rate of approximately 50 patients per month. The overall study duration will be approximately 28 months.

RANDOMIZATION
Patients will be randomized in a double-blind fashion using a 1:1 allocation of patients to either sorafenib in combination with gemcitabine and cisplatin (sorafenib group), or placebo in combination with gemcitabine and cisplatin (placebo group).
Stratification factors for the randomization are:
• Performance status (PS): ECOG (Eastern Cooperative Oncology Group) PS 0 vs. (versus) 1
• Stage: IIIB with effusion vs. Stage IV

Patients will be randomized to one of the following 2 treatment groups:
Sorafenib Group- Gemcitabine 1250 mg/m2 iv (intravenous) on days 1 and 8 and

cisplatin 75 mg/m2 iv on day 1, q (every) 3 weeks for up to 6 cycles, plus sorafenib 400 mg po (per os, taken orally) bid days 1-21
Placebo Group- Gemcitabine 1250 mg/m2 iv on days 1 and 8 and cisplatin 75 mg/m2 iv on day 1, q 3 weeks for up to 6 cycles, plus placebo po bid days 1-21
The dose of all three drugs may be adjusted or delayed for an individual patient based on toxicities that are related to protocol therapy. Cisplatin and gemcitabine will be administered for up to 6 cycles (Chemotherapy Phase). Thereafter, patients continue sorafenib or placebo as a single agent (Maintenance Phase) until tumor progression or other criteria for withdrawal are met. Although sorafenib and placebo are dosed continuously (twice daily) in the Maintenance Phase, cycle lengths continue defined as 21 days, and sorafenib or placebo are administered on days 1-21 of each 21-day cycle.

Intervention

Patients will be randomized to one of the following 2 treatment groups:

1. Sorafenib Group
- Gemcitabine 1250 mg/m2 iv (intravenous) on days 1 and 8 (up to 6 cycles)
- Cisplatin 75 mg/m2 iv on day 1 (up to 6 cycles)
- Sorafenib 400 mg taken orally bid days 1-21

2. Placebo Group
- Gemcitabine 1250 mg/m2 iv (intravenous) on days 1 and 8 (up to 6 cycles)
- Cisplatin 75 mg/m2 iv on day 1 (up to 6 cycles)
- Placebo taken orally bid days 1-21

Study burden and risks

Besides the study medication, there may be other risks or discomforts in the study.

CT scans: exposure to radiation. These CT scans would normally be done to determine if the disease is spreading, hence the patient will no be exposed to additional radiation just because of participating in the study. However, depending on the tumor*s response to the drugs, additional CT scans may be performed.

Bloodsamples:drawing blood or inserting the needle in the arm for the treatment may cause pain, bruising, lightheadedness, local skin reactions and on rare occasions, infection. Seepage of fluids into the surrounding tissue during intravenous infusions may cause discomfort.

It is not known if the patient will have any benefit from sorafenib. The patient may not receive sorafenib at all if the patient has been assigned to receive placebo. It is hoped that, through this study, it can be proven that

patients with Non-Small Cell Lung Cancer will live longer without disease progression by using sorafenib as an additional treatment to chemotherapy.

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. Stage IIIB (with cytologically confirmed malignant pleural or pericardial effusion) or Stage IV histological or cytological confirmation of NSCLC of non-squamous subtype. (thoracentesis or pericardiocentesis is not necessary if a biopsy of the original tumor is available to confirm diagnosis of NSCLC)
2. Patients with at least one measurable lesion. Lesions must be measured by CT-scan or MRI (Magnetic resonance imaging) according to Response Evaluation Criteria in Solid Tumors (RECIST)
3. Adequate bone marrow, liver and renal function

(for more detailed information about the in- en exclusion criteria see protocol page 14-17 and Am 6, version 2)

Exclusion criteria

1. Cardiac disease: Congestive heart failure > NYHA class 2; Patients must not have unstable angina or CAD or myocardial infection within the past 6 months.
2. Cardiac arrhythmias requiring anti-arrhythmic therapy
3. Uncontrolled hypertension defined as systolic blood pressure >150 mmHg or diastolic pressure > 90 mm Hg; despite optimal medical management
4. Seizure disorder requiring medication
5. Known brain metastases. patients with neurological symptons should undergo a CTA scan/MRI over the brain to exclude brain metastases
6. History of organ allograft
7. Patients with evidence or history of bleeding diathesis or coagulopathy
8.Uncorrected dehydration
9. Known or suspected allergy to the investigational agent or any agent given in association with this trial.
10. NSCLC patients with squamous cell carcinoma diagnosis documented either by cytology or biopsy.;Excluded therapies and medications, previous and concomitant
1. Any prior systemic anticancer therapy including cytotoxic therapy, targeted agents, experimental therapy, adjuvant, or neo-adjuvant therapy for NSCLC
2. Radiotherapy during study or within 3 weeks of start of study drug. (Palliative radiotherapy will be allowed as described in the Prior and Concomitant Therapy section)
3. Major surgery, open biopsy or significant traumatic injury within 4 weeks of first dose of study drug (bronchoscopy is allowed)
4. Investigational drug therapy outside of this trial during or within 4 weeks of study entry;(for more detailed information about the in- en exclusion criteria see protocol page 14-17 and Am 6, version 2)

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):	22-02-2007
Enrollment:	55
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	cisplatin
Generic name:	cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemzar®
Generic name:	gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nexavar®
Generic name:	sorafenib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-11-2006
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

Approved WMO

Date:	27-12-2006
Application type:	First submission
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

Approved WMO Date:	29-03-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	19-04-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	13-11-2007
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	07-03-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	18-04-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	22-04-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	17-07-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	18-07-2008
Application type:	Amendment

Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	13-08-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	28-10-2008
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	31-07-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	12-08-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	09-10-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	21-10-2009
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	17-05-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO	

Date:	26-05-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	19-07-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	20-07-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	06-09-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)
Approved WMO Date:	09-09-2010
Application type:	Amendment
Review commission:	IRB Amsterdam: Independent Review Board Amsterdam (Amsterdam)

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	EUCTR2006-002688-26-NL
CCMO	NL14907.003.06