A Randomized, Double-blind, Multi-center Phase 2 Trial of Denosumab in Combination With Chemotherapy as First-line Treatment of Metastatic Non-small
Cell Lung Cancer

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This study will be carried out to gain more knowledge about denosumab in patientes with NSCLC. The effect of denosumab in combination with platinum-doublet chemotherapy in patients with NSCLC and the relation with the presence of biomarkers in...

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

Summary

ID

NL-OMON45036

Source
ToetsingOnline

Brief title
20120249

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Metastatic lung cancer

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Denosumab, Non-small cell lung cancer, Tumor RANK expression

Outcome measures

Primary outcome

To estimate the treatment effect of the combination of denosumab and standard

of care (SOC) versus SOC alone on overall survival (OS).

Secondary outcome

To assess whether any relative benefit on OS from the combination of denosumab

and SOC versus SOC alone in NSCLC is associated with tumor RANK expression

Study description

Background summary

Post-hoc analysis of a lung canccer subset in other studies suggested an advantage in overall survival in teh comaprison of denosumab vs. zoledronic acid. In addition, there is an unmet medical need for molecularly targeted therapies in metastatic NSCLC.

Study objective

This study will be carried out to gain more knowledge about denosumab in patientes with NSCLC. The effect of denosumab in combination with platinum-doublet chemotherapy in patients with NSCLC and the relation with the presence of biomarkers in tumorcells will be studied.

Study design

The study consists of 2 patrts:

1) Screening
Patients will undergo study assessmnets to check if in and exclusion criteria are fullfilled. Eligble patients will start the treatment phase

2) Treatment phase
Patients will be randomised (2:1) in one of the following arms:
- Arm 1: denosumab 120 mg subcutaneous 4-weekly or 3-weekly + loading dosis on day 8 + 4-6 cycli standard chemotherapy
- Arm 2: placebo subcutaneous 4-weekly or 3-weekly + loading dosis on day 8 + 4-6 cycli standard chemotherapy

144 patients will be randomised in arm 1 and 72 in arm 2. In total 216 subjects will participate in teh study.

After 4-6 cycli, subjects randomized in arm 1 will receive denosumab 120 mg subcuteneous 4-weekly or 3-weekly and standard chemotherapy (as maintenance therapy of extra cycli). Patients randomised in arm 2 receive placebo subcuteneous 4-weekly or 3-weekly and standard chemotherapy (as maintenance therapy of extra cycli). All patients receive calcium and vitamin D supplements during the treatment phase

The treatment phase ends whne the primary endpoint has been raeched, the patient has died or is lost to follow up.

Added in protocol amendment 2: If denosumab is determined to have a positive benefit:risk profile in this study, all subjects currently undergoing scheduled assessments will be offered open-label denosumab at a dose of 120 mg SC for up to 2 years. If the benefit:risk profile is not positive, all subjects will be followed for up to 2 years after the last dose of blinded investigational product.

Intervention

Eligible patients will be treated with denosumab 120 mg subcutaneous 4-weekly or 3-weekly + 4-6 cycli van standard chemotherapy or placebo subcutaneous 4-weekly or 3-weekly + 4-6 cycli van standard chemotherapy

Study burden and risks

Risk: adverse events of denosumab. During the visits to the hospital the subjects will be monitored for adverse events.
Burden: maximum study duration is about 5 years. The subject will visite the hosppital every 3-4 weeks. The duration of each visit will vary from 3-4 hours

Contacts

Public
Amgen

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Scientific
Amgen

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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 or cytologically confirmed stage IV non-small cell lung carcinoma (NSCLC), according to 7th TNM classification (cytological specimens obtained by bronchial washing or brushing, or fine-needle aspiration are acceptable)
- Subject has available and has provided consent to release to the sponsor (or designee) a tumor block with confirmed tumor content (or approximately 20 unstained charged slides [a minimum of 7 slides is mandatory]) and the corresponding pathology report
- Planned to receive 4 to 6 cycles of pemetrexed or gemcitabine in combination with cisplatin or carboplatin
* For subjects to receive pemetrexed, planned to receive vitamin B12 and folate per pemetrexed approved labeling
- Radiographically evaluable (measurable or non-measurable) disease (according

to modified RECIST 1.1 criteria, Appendix E)
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Male or female subjects * 18 years of age at the time of screening
- Adequate organ function, as defined by the following criteria:
*Serum aspartate aminotransferase (AST) * 2.5 x upper limit of normal (ULN) (or AST * 5 x upper limit of normal (ULN) if liver metastases are present)
*Serum alanine aminotransferase (ALT) * 2.5 x ULN (or ALT * 5 x upper limit of normal (ULN) if liver metastases are present)
*Serum total bilirubin (TBL) * 1.5 x ULN (or * 2.0 x upper limit of normal (ULN) if liver metastases are present)
*Creatinine clearance * 45 mL/min (refer to section 6.3.1.3 for Cockcroft*Gault formula)
- Serum calcium or albumin-adjusted serum calcium * 2.0 mmol/L
- Expected life expectancy of at least 3 months
- Subject has provided or subject*s legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated

Exclusion criteria

- Known presence of documented sensitizing epidermal growth factor receptor (EGFR) activating mutation or EML4-ALK translocation (screening following local standards, but strongly encouraged in non-squamous histology)
- Known brain metastases (systematic screening of patients not mandatory)
- Prior systemic therapy for the treatment of NSCLC (including chemoradiation), except if for non-metastatic disease and was completed at least 6 months prior to randomization
- Planned to receive bevacizumab
- Central (chest) radiation therapy within 28 days prior to randomization, radiation therapy to any other site(s) within 14 days prior to randomization
- Prior administration of denosumab
- Subjects with sarcomatoid, carcinoid, and mesenchymal histologies
- More than 1 year of cumulative oral bisphosphonate usage prior to randomization
- More than 1 previous dose of IV bisphosphonate administration prior to randomization
Please refer to pga 24 of the protocol

Study design

Design

Study phase: 2

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):	12-03-2014
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	XGEVA
Generic name:	Denosumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-09-2013
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-10-2013
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-02-2014
Application type:	Amendment
Review commission:	METC St Elisabeth Ziekenhuis (Tilburg)
Approved WMO	

Date:	11-02-2014
Application type:	Amendment
Review commission:	METC St Elisabeth Ziekenhuis (Tilburg)
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-09-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-10-2015
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-07-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-10-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	119157
EudraCT	EUCTR2013-001662-42-NL
CCMO	NL45573.008.13