PLEASE NOTE: *This study has been imported from ClinicalTrials.gov without additional data checks.*

Trial Description

Title

Open-label,Random.,Controlled,Multicenter Phase II Study Investigating 2 Cilengitide Regimens in Combination w/ Cetuximab & Platinum-based Chemotherapy Compared to Cetuximab & Platinum-based Chemotherapy Alone as 1st-line Treatment for Patients w/ Advanced NSCLC

Trial Acronym

CERTO

URL of the trial

[---]*

Brief Summary in Lay Language

Primary objective of the study's Safety run-in:

- To determine the MTD of cilengitide in combination with cetuximab, and platinum-based chemotherapy (cisplatin/vinorelbine or cisplatin/gemcitabine).

Primary objective of the study's Randomization Part:

- To assess the efficacy of cilengitide in combination with cetuximab and platinum-based chemotherapy (cisplatin/vinorelbine or cisplatin/gemcitabine) compared to cetuximab and platinum-based chemotherapy alone in terms of progression-free survival (PFS) time.

Study design and plan:

This is a multicenter, open-label, randomized, controlled Phase II study with a safety run-in part in subjects with advanced non-small cell lung cancer (NSCLC).

During the safety run-in, the regimen was intensified stepwise by cohort (cilengitide i.v. 1000 mg to 2000 mg twice a week) in a classical 3+3 subjects (for each platinum-based chemotherapy regimens separately) approach with predefined dose- and schedule reduction rules.

In the safety run-in 12 subjects were included and evaluated for safety and

feasibility of different escalating doses of cilengitide administered twice weekly in combination with cetuximab, cisplatin and vinorelbine or gemcitabine.

In the safety run-in a dose of 2000 mg cilengitide twice weekly was well tolerated for each of the platinum based chemotherapy regimens (cisplatin/vinorelbine or cisplatin/gemcitabine) in combination with cetuximab.

After completion of the safety run-in, the randomized part has been started, during which all subjects will receive cetuximab and platinum-based chemotherapy (cisplatin/vinorelbine or cisplatin/gemcitabine).

Subjects will be centrally randomized on a 1:1 basis to either Group A or C; Group B will be closed with implementation of Amendment No. 4 (dated 20 December 2010):

• Group A: Cilengitide 2000 mg once weekly (Days 1, 8, and 15 of every 3-week chemotherapy cycle) in combination with cetuximab and platinum-based chemotherapy that will consist of the following:

- Cetuximab once weekly (Days 1, 8, and 15), plus cisplatin on Day 1 and vinorelbine on Days 1 and 8 of every 3-week chemotherapy cycle, or

- Cetuximab once weekly (Days 1, 8, and 15), plus cisplatin on Day 1 and gemcitabine on Days 1 and 8 of every 3-week chemotherapy cycle.

The decision which of the 2 chemotherapy regimens will be applied for a given subject is at the discretion of the treating investigator.

• Group B: Cilengitide 2000 mg twice weekly (Days 1, 4, 8, 11, 15, and 18 of every 3-week chemotherapy cycle) in combination with cetuximab and platinum-based chemotherapy as described for Group A.

Group B will be closed with implementation of Amendment No. 4 (global, dated 20 December 2010). Subjects randomized to Group B before implementation of Amendment No 4 will continue to be treated as planned.

• Group C: Cetuximab and platinum-based chemotherapy as described for Group A

Chemotherapy will be given until radiographically documented progressive

**disease (PD) or
unacceptable toxicity but for no more than 6 cycles.**

**Cilengitide and cetuximab will be given until radiographically documented PD or unacceptable
toxicity.**

**Randomization will be performed centrally using an interactive voice/web response system
(IXRS). A stratified block randomization procedure will be employed using chosen first-line
chemotherapy (cisplatin/vinorelbine versus cisplatin/gemcitabine) as stratification
criterion.**

Brief Summary in Scientific Language

Schedule of visits and assessments:

Pre-screening Visit (Within 2 weeks prior to screening):

**In an initial step subjects with newly diagnosed NSCLC (suspected or already established
diagnosis) will be offered to have their tumor assessed locally for EGFR expression. After
giving specific written informed consent to this analysis, they will be formally registered
and the tissue will be analyzed.**

**Signing of informed consent for local IHC-based EGFR expression determination; EGFR
expression testing in local pathology laboratory using archived tumor material;
Demographics, i.e. subject initial, date of birth, gender, ethnicity/race, height;
Allocation of subject number; Date of initial diagnosis; Tumor characteristics (histology,
localization, metastasis, Tumor-Nodes-Metastases (TNM) classification).**

Screening Visit (Within 3 weeks prior to randomization):

**Signing of informed consent for study participation (only if pre-screening positive and with
an EGFR expression ≥ 200); Archived tumor material for biomarker analysis including EGFR,
k-ras, b-raf, pathology and possible additional biomarker research including mutation
testing; Relevant medical history; Prior treatment of underlying tumor; Physical examination
including vital signs (including body weight, without BSA); ECOG-performance status; Central
12-lead ECG; Pulmonary function test; Baseline imaging within 4 weeks prior to randomization
(RECIST): At least chest + abdomen CT (or MRI if there are contraindications to CT);
Documentation of concomitant medications and AEs; Safety laboratory assessments (hematology**

including coagulation parameters and biochemistry); Blood sampling for HACA assessment;
Serum pregnancy test for women of childbearing potential within 7 days to the start of study
medication; In-/exclusion criteria review; Randomization, (to be performed ≤7 days before
start of therapy); Optional: additional written informed consent for pharmacogenetics
testing and optional: blood sampling for pharmacogenetics testing (only applicable for
randomized study part).

Day 1 of Each Cycle (Start of Cycle Visit) (At start of each chemotherapy cycle) Before
start of first cycle: randomization should be performed ≤7 days before start of therapy;
Physical examination including vital signs (including body weight and BSA); Assessment of
cardiovascular specific symptoms; Documentation of AEs; Concomitant medication; Safety
laboratory assessments (hematology including coagulation parameters and biochemistry) must
be available before start of chemotherapy; Central Holter ECG before start of treatment
until the end of infusion of cilengitide (for Group C subjects until the 1 hour after the
end of infusion of cetuximab) on Day 1 of the first cycle only; Central standard ECG Cycles
2-6; ECOG-performance status; Administration of cilengitide (Groups A and B); Administration
of cetuximab (all subjects); Administration of cisplatin/vinorelbine or
cisplatin/gemcitabine (all subjects; first 6 cycles only); Blood sampling for plasma
circulating markers (only on Day 1 of Cycle 1 at pre-dose and at the end of the cisplatin
infusion); Additional blood sampling for CTC/CEC assessment (only pre-dose on Day 1 of Cycle
1 and Cycle 2); Blood sampling for cilengitide PK (6-10 subjects of Group B only; Cycle 1
only; see Section 7.4.1 for details) (at dedicated sites only); Blood sampling for cetuximab
PK (all subjects of Group A only; Cycles 1 and 2 only; see Section 7.4.1 for details); Blood
sampling for vinorelbine PK (6-10 subjects of Groups B and C; Cycle 1 only; see Section
7.4.1 for details) (at dedicated sites only).

DAYS 4, 11 and 18

Days 4, 11, and 18 of Each Cycle (Group B only) Vital signs (without BSA/body weight);
Administration of cilengitide.

Days 4 and 11 (additional examinations during the first 2 weeks of first cycle of safety

run-in): safety laboratory assessments (hematology including coagulation parameters and biochemistry).

DAYS 8 and 15

Days 8 and 15 of Each Cycle: Vital signs (without BSA/weight); assessment of cardiovascular specific symptoms; documentation of AEs; concomitant medication; administration of cilengitide (Groups A and B); administration of cetuximab; administration of vinorelbine or gemcitabine (all subjects; Day 8 of the first 6 cycles only); blood sampling for proBNP (Cycle 1 Day 8 only); blood sampling for cetuximab PK (all subjects of Group A only; Days 8 and 15 of Cycle 1 and Day 8 of Cycle 2 only); blood sampling for plasma circulating markers (all subjects; Days 8 and 15 of first cycle only at pre dose, for each subsequent cycle on Day 8 only).

Days 8 and 15 (additional examinations during safety run-in): safety laboratory assessments (hematology including coagulation parameters and biochemistry) must be available before start of chemotherapy.

Once weekly safety lab evaluation during safety run-in (after end of chemotherapy): safety laboratory assessments (hematology including coagulation parameters and biochemistry).

6-weekly Evaluation Visit (Every 6 weeks +/- 2 days after randomization until final tumor assessment (FTA) visit): Physical examination including vital signs (without BSA/weight); assessment of cardiovascular specific symptoms; documentation of AEs; concomitant medication; ECOG-performance status; central standard ECG after cycle 6 only; CT scan or MRI; safety laboratory assessments (hematology including coagulation parameters and biochemistry); serum pregnancy test for women of childbearing potential. Blood sampling for plasma circulating markers during maintenance treatment only, and for CTC/CEC (only once after 6 cycles of chemotherapy).

Final Tumor Assessment Visit (At occurrence of PD and/or before start of any other systemic anti-tumor therapy): Physical examination including vital signs (without BSA); documentation of AEs; concomitant medication; ECOG-performance status; CT scan or MRI; safety laboratory

assessments (hematology including coagulation parameters and biochemistry); blood sampling for plasma circulating markers and CTC/CEC; serum pregnancy test.

End-of-Study (EoS) Visit (Around 28 days after the last investigational medicinal product [cilengitide or cetuximab] administration, or before other anticancer treatment starts, but not before the FTA visit): Physical examination including vital signs (without BSA); documentation of AEs. If a subject begins a subsequent anticancer therapy, the AE reporting period for non-serious AEs will end at the time the new treatment starts; ECOG-performance status; concomitant medication; safety laboratory assessments (hematology including coagulation parameters and biochemistry); blood sampling for HACA assessment; central 12-lead ECG; reason for discontinuation.

Survival Follow-up (Every 2 months after EoS visit): Each subject's survival status and any further anti-cancer treatments will be documented every 2 months after the end of study visit until death, loss to follow-up, or consent withdrawal.

All subjects will be treated with platinum-based chemotherapy for a maximum of 6 cycles (i.e. 18 weeks), until PD or death, unacceptable toxicity, or until the subject withdraws consent. Subjects who do not experience PD after 6 cycles of platinum-based treatment will continue treatment with cilengitide (Groups A and B) and cetuximab (Group A, B and C). Subjects who discontinue treatment without PD will remain on study. Response assessment will continue every 6 weeks until PD or until other anti-tumor treatment is started. Upon this occurrence, all study medication should be discontinued and a final tumor assessment (FTA) visit will be carried out. The end-of-study visit should be performed around 4 weeks after the last investigational medicinal product administration but not before the FTA visit.

Organizational Data

- DRKS-ID: **DRKS00003822**
- Date of Registration in DRKS: **2012/05/04**
- Date of Registration in Partner Registry or other Primary Registry: **2009/02/10**
- Investigator Sponsored/Initiated Trial (IST/IIT): **no**
- Ethics Approval/Approval of the Ethics Committee: **[---]***
- (leading) Ethics Committee Nr.: **[---]***

Secondary IDs

- EudraCT-No.
(for studies acc. to Drug Law): **2008-004148-35**
- Primary Registry-ID: **NCT00842712 (ClinicalTrials.gov)**
- Sponsor-ID: **EMR 200037-014 (Merck KGaA)**
- Other Secondary-ID: **EudraCT Number: 2008-004148-35**

Health condition or Problem studied

- Free text: **NSCLC**
- Free text: **Non Small Cell Lung Cancer**
- ICD10: **C34 - Malignant neoplasm of bronchus and lung**

Interventions/Observational Groups

- Arm 1: **Drug: Cilengitide**
- Arm 2: **Drug: Cilengitide, Cetuximab and platinum-based chemotherapy**

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **[---]***
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **I-II**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **[---]***

Primary Outcome

- Safety run-in: Occurrence of any DLT within a subject during the first 3 weeks of treatment (first chemotherapy cycle).; time frame: In the first 3 weeks of treatment
- Randomized Part: Progression Free Survival Time; time frame: duration of the

trial (24 months)

Secondary Outcome

- Randomized Part: - Overall survival time - Best overall response - Time to treatment failure; time frame: duration of the trial (24 months)

Countries of recruitment

- BE **Belgium**
- CZ **Czech Republic**
- FR **France**
- DE **Germany**
- IE **Ireland**
- IT **Italy**
- PL **Poland**
- ES **Spain**

Locations of Recruitment

- **Research Site, Aachen**
- **Research Site, Berlin**
- **Research Site, Darmstadt**
- **Research Site, Frankfurt**
- **Research Site, Freiburg**
- **Research Site, Goch**
- **Research Site, Halle-Dölau**
- **Research Site, Hamburg**
- **Research Site, Luebeck**
- **Research Site, Mannheim**
- **Research Site, Munic**
- **Research Site, Offenbach**
- **Research Site, Oldenburg**
- **Research Site, Wiesbaden**

Recruitment

- Planned/Actual: **[---]***
- (Anticipated or Actual) Date of First Enrollment: **2009/02/27**
- Target Sample Size: **164**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

Inclusion criteria:

1. Written informed consent obtained before undergoing any study-related activities.

2. Male or female, at least 18 years of age.

3. Histologically confirmed NSCLC, stage IIIb with documented malignant pleural effusion or stage IV (according to staging system 6th edition).

4. EGFR expression ≥ 200 on tumor tissue determined by local testing using the kit and testing procedures described in the study MOP.

5. Archived tumor material sample for central histology and further biomarker research including mutational analysis of genes such as EGFR, k-ras, b-raf (material details described in the study MOP).

6. At least 1 radiographically documented measurable lesion in a previously non-irradiated area according to evaluation criteria in solid tumors (RECIST), i.e. this lesion must be adequately measurable in at least 1 dimension (longest diameter [LD] to be recorded) as ≥2 cm by conventional techniques or ≥1 cm by spiral CT scan.

7. Eastern Cooperative Oncology Group (ECOG)-performance status 0-1.

8. Leukocyte count ≥ 3.0 x 10(9)/L.

9. Absolute neutrophil count (ANC) ≥1.5 x 10(9)/L.

10. Platelets ≥100 x 10(9)/L.

11. Hemoglobin ≥9 g/dL (without transfusions).

12. Bilirubin ≤1.5 x upper limit of normality (ULN).

13. AST ≤5 x ULN and ALT ≤5 x ULN.

14. Serum creatinine ≤1.25 x ULN and/or creatinine clearance ≥60 mL/min.

15. Prothrombin time (PT), international normalized ratio (INR) within normal limits and partial thromboplastin time (PTT) below upper limit of normal.

16. Sodium and potassium within normal limits or ≤10% above or below (supplementation permitted).

17. Effective contraception for both male and female subjects (if the risk of conception exists).

1. If female, she must:

- be neither pregnant nor breast-feeding, nor attempting to conceive and

- use a highly effective method of contraception for at least 7 days before entry into the trial, throughout the entire duration of the trial and for 6 months following completion of the last dose of trial medication. A highly effective method of contraception is defined as those which result in a low failure rate (i.e. less than1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, IUDs (hormonal or copper-based), sexual abstinence or vasectomized partner, or

- be post-menopausal or surgically sterilized 2. If male, he must be willing to use contraception to avoid pregnancies for at least 7 days before entry into the trial, throughout the entire duration of the trial and for 6 months following the last dose of trial medication. Two negative semen analyses post-vasectomy have to be available in order to be considered infertile.

Exclusion criteria

Exclusion criteria:

1. Prior treatment with an antibody or molecule targeting EGFR- and/or vascular

endothelial growth factor receptor (VEGFR)-related signaling pathways.

2. Previous chemotherapy for NSCLC including prior adjuvant therapy.

3. History of or current brain metastasis and/or leptomeningeal disease (known or suspected).

4. Radiotherapy (except localized radiotherapy for pain relief), major surgery or any intake of investigational drug in the 30 days before the start of study treatment entry.

5. Concurrent chronic immunosuppressive or hormone anti-cancer therapy (physiologic hormone replacement or corticosteroid treatment for COPD is allowed).

6. Clinically relevant coronary artery disease (New York Heart Association [NYHA] functional angina classification III/IV), congestive heart failure (NYHA III/IV), clinically relevant cardiomyopathy, history of myocardial infarction in the last 12 months, or high risk of uncontrolled arrhythmia.

7. History of coagulation disorder associated with bleeding, recurrent or recent thrombotic events or history of hemoptysis related to bronchopulmonary cancer. Hemoptysis is defined as coughing more than a teaspoon of red blood per day.

8. Recent peptic ulcer disease (endoscopically proven gastric, duodenal or esophageal ulcer) within 6 months of study treatment start.

9. Presence of any contra-indication to treatment with cilengitide, cetuximab, cisplatin and vinorelbine or gemcitabine including:

- **Known hypersensitivity to cilengitide, cetuximab, cisplatin, vinorelbine, or gemcitabine or to any of the excipients of these drugs.**
- **Superior vena cava syndrome contra-indicating hydration.**
- **Symptomatic peripheral neuropathy NCI-CTCAE Grade ≥2 and/or ototoxicity NCI CTC AE Grade ≥2, except if due to trauma or mechanical impairment due to tumor mass.**
- **Phenytoin (introduced to prevent the anticonvulsant effect of certain anticancer drugs) (contra-indication for cisplatin).**

- Yellow Fever Vaccine, Live Attenuated Vaccines (contra-indications for cisplatin).

10. Pregnancy or lactation period.

11. Concurrent treatment with a non-permitted drug (see Section 6.8).

12. Treatment with any other investigational product within the past 30 days.

13. Previous malignancy other than NSCLC in the last 5 years except for basal cell cancer of the skin or pre-invasive cancer of the cervix.

14. Medical or psychological conditions that would not permit the subject to complete the study or sign informed consent.

15. Signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffer(ed) from such.

16. Patients with hepatitis, massive liver metastases (> 75 %), current alcoholism or liver cirrhosis (because of vinorelbine and gemcitabine).

17. Patients who have been therapeutically anticoagulated

18. Legal incapacity or limited legal capacity.

19. Significant disease (e.g. interstitial lung disease) which, in the investigator's opinion, would exclude the subject from the study.

Addresses

■ **Primary Sponsor**

Merck KGaA

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

■ **Contact for Scientific Queries**

Merck KGaA
Medical Responsible

Contact for Scientific Queries

Merck KGaA
Medical Responsible

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

- **Contact for Public Queries**

Merck KGaA
Medical Responsible

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Sources of Monetary or Material Support

- **[---]***

Bitte wenden Sie sich an den Sponsor / Please refer to primary sponsor

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2013/07/01**

Trial Publications, Results and other documents

The parameters in ClinicalTrials.gov and DRKS are not identical. Therefore the data import from ClinicalTrials.gov required adjustments. For full details please see the DRKS FAQs.

- Translation on version: 9

- Last processed date by ClinicalTrials.gov: 2013/10/30

* *This entry means the parameter is not applicable or has not been set.*

*** *This entry means that data is not displayed due to insufficient data privacy clearing.*