An Open-label, Multicenter, Randomized Phase 2 Study Evaluating the Safety and Efficacy of Cisplatin and Pemetrexed With or Without Cixutumumab as First Line Therapy in Patients with Advanced Nonsquamous Non Small Cell Lung Carcinoma

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

Summary

ID

NL-OMON38158

Source
ToetsingOnline

Brief title
JAEM (219-390)

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eli Lilly
Source(s) of monetary or material Support: Eli Lilly and Company

Intervention

Keyword: Cisplatin, Cixutumumab, Lung Cancer, Pemetrexed

Outcome measures

Primary outcome

Criteria for Evaluation:

Efficacy:

• Progression-free survival is defined as the time from the date of randomization until the date of objectively determined date of progression as defined by RECIST v. 1.1, or death from any cause, whichever is first.

• Overall response rate is defined as the proportion of all randomized patients with measurable disease with the best response of partial response (PR) or complete response (CR) according to RECIST v. 1.1 in a given arm.

• Time to progressive disease is defined as the elapsed time in days from the date of randomization to the first date of objective progression of disease.

• Change in tumor size is defined as the change from baseline measurement to the measurement at the end of cycle 2, as assessed using radiographic imaging. If CTS is observed after 2 cycles, the log ratio of tumor size at Visit 2 to tumor size at baseline will be calculated for each patient.

• Overall survival is defined as the time from the date of randomization to the date of death from any cause.

• Duration of response is defined as the time measurement criteria are first met for confirmed PR/CR (whichever is first recorded) until the first date that the criteria for progressive disease is met or death.

Safety:

• Adverse event (AE) grading (Common Terminology Criteria for Adverse Events [CTCAE] v. 4.0)

• Laboratory investigations (hematology/clinical chemistry)

• Concomitant medications assessments

• Physical examinations/vital signs

Health Outcomes:

• For each of the LCSS items: Time to worsening symptoms is defined as the time from the date of randomization to the first date of worsening.

Pharmacokinetic/Pharmacodynamic:

• Standard pharmacokinetic analysis (Arm B only)

• Pharmacodynamic markers: including, but not limited to, free IGF-I, total IGF-I, IGFBP-3

Translational research:

• Immunohistochemical analysis: including, but not limited to, IGF-IR mutational analysis: including, but not limited to, p53, KRAS, and EGFR Gene copy number: IGF-IR Gene promoter methylation (IGFBP 3)

• Single nucleotide polymorphisms (SNPs) in IGF system-related genes

• Gene expression analysis: including, but not limited to, IGFBP-3, IGF-IR, insulin receptor, IGF-I, and IGF-II.

Secondary outcome

Not applicable

Study description

Background summary

Study Rationale
Over half of all patients with non-small cell lung cancer (NSCLC) present with advanced stage disease. Chemotherapy, usually employing platinum-based agents (cisplatin, carboplatin) in combination with other agents (including but not limited to paclitaxel, docetaxel, vinorelbine, and gemcitabine), is the initial choice for patients with advanced NSCLC; combination chemotherapy of this type may extend expected median overall survival (OS) to 10.3 months. Though improvements in survival have been observed in recent years as a result of the availability of newer agents, these improvements have been modest and the mainstay of treatment in most countries continues to be platinum-based chemotherapy doublets. Further exploration of the efficacy of both current and new treatments is needed in patients with advanced NSCLC.
The combination of pemetrexed with cisplatin has shown promising activity as a first-line treatment for advanced NSCLC. In a Phase 3 study, pemetrexed/cisplatin showed similar efficacy to gemcitabine/cisplatin as first-line treatment of advanced NSCLC, with an overall survival (OS) of 10.3 months in both arms. In a preplanned subset analysis, pemetrexed/cisplatin showed statistically superior OS over gemcitabine/cisplatin in patients with NSCLC other than predominantly squamous cell histology (11.0 months versus 10.1 months). Based on the results of this study, pemetrexed in combination with cisplatin is now a standard of care for the first-line treatment of patients with locally advanced or metastatic NSCLC with nonsquamous histology.
The upregulation or overexpression of the insulin-like growth factor-I receptor (IGF-IR), often in concert with overexpression of IGF ligands, can lead to the potentiation of receptor signaling and the enhancement of cell proliferation and survival. As a result, targeting and inhibiting the IGF-IR pathway is an attractive anticancer therapeutic strategy. Cixutumumab possesses high affinity for IGF-IR and acts as an antagonist of IGF-I and IGF-II ligand binding and signaling. In NSCLC xenograft models, cixutumumab in combination with pemetrexed plus cisplatin demonstrated a statistically significant increase in antitumor activity compared to pemetrexed plus cisplatin alone. Thus, the addition of cixutumumab to the combination therapy of cisplatin and pemetrexed for the treatment of patients with advanced NSCLC may result in improved patient outcomes.

Study objective

The primary objective of this study is to evaluate the hypothesis that cixutumumab given in combination with cisplatin and pemetrexed is superior to cisplatin and pemetrexed as first-line therapy for patients with advanced nonsquamous non-small cell lung carcinoma (NSCLC) as measured by progression-free survival (PFS).

The secondary objectives of the study are:
• to evaluate the hypothesis that cixutumumab given in combination with cisplatin and pemetrexed is superior to cisplatin and pemetrexed, as measured by the following:
o Objective response rate (ORR)
o Time to progressive disease (TTPD)
o Change in tumor size (CTS)
o Overall survival (OS)
o Duration of response
• to evaluate the safety profile of cixutumumab given in combination with cisplatin and pemetrexed
• to assess the pharmacokinetic profile of cixutumumab (Arm B only)
• to assess the immunogenicity of cixutumumab (Arm B only)
• to assess the pharmacodynamic profile of cixutumumab, including:
o potential surrogates of cixutumumab pharmacodynamic activity including, but not limited to, free IGF-I, total IGF-I, IGFBP-3
• to evaluate the time to worsening symptoms (TWS) as measured by Lung Cancer Symptom Scale (LCSS) scores (patient scale only)

Additional exploratory biomarker objectives of the study are as follows:
• Characterize single-nucleotide polymorphisms, DNA mutations, RNA analysis, and copy number variation in IGF-IR and other pathway-related genes, relevant to the safety, efficacy, and mechanism of action of cixutumumab in germ-line DNA and tissue; and,
• Investigate the association between biomarkers and clinical outcome

Study design

Study Design: This is an open-label, multicenter, randomized, Phase 2 trial in which patients with advanced
nonsquamous NSCLC receive cisplatin and pemetrexed with or without cixutumumab as first-line
therapy. Approximately 220 patients will be randomized in a 1:1 ratio to 1 of 2 treatment arms as follows:
* Arm A - cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 every 21 days
* Arm B - cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 plus cixutumumab 20 mg/kg every 21 days.
Randomization will be stratified by gender, smoking status, and Eastern

Cooperative Oncology Group (ECOG)
performance status. After discontinuation of cisplatin treatment (maximum of 4 to 6 cycles), maintenance therapy
may continue as follows:
* Arm A - pemetrexed 500 mg/m2 every 21 days
* Arm B - pemetrexed 500 mg/m2 plus cixutumumab 20 mg/kg every 21 days.

Intervention

Approximately 220 patients will be randomized in a 1:1 ratio to 1 of 2 treatment arms as follows:
• Arm A - cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 every 21 days
• Arm B - cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 plus cixutumumab 20 mg/kg every 21 days.
Randomization will be stratified by gender, smoking status, and Eastern Cooperative Oncology Group (ECOG) performance status. After discontinuation of cisplatin treatment (maximum of 4 cycles), maintenance therapy may continue as follows:
• Arm A - pemetrexed 500 mg/m2 every 21 days
Arm B - pemetrexed 500 mg/m2 plus cixutumumab 20 mg/kg every 21 days.

Study burden and risks

A detailed overview of side effects of cixutumumab is included in appendix 2 of the patient infiormation sheet. Very common side effects are:
a lack of energy and high blood glucose levels. Common side effects are amongst others: diabetes, blurrred vision, nausea, fever, weight decrease, liver function abnormalities, loss of apetite, shortness of breat, dizzyness and headache.

Furthermore patients could find discomfort during the study procedures: bloodtests, MRI-scan and CT-scan. We refer to appendix 2 of the patient information sheet for a more detailed overview of the possible discomforts of these procedures.

Contacts

Public
Eli Lilly

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Indianapolis Indiana 46285
US
Scientific

Eli Lilly

Lilly Corporate Center 1
Indianapolis Indiana 46285
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients will be at least 18 years old with histologically or cytologically confirmed Stage IV (AJCC edition 7) nonsquamous NSCLC. Patients may have either measurable or nonmeasurable disease based on the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v. 1.1), and must have ECOG status of 0 or 1 as well as adequate hematologic, coagulation, and organ function. Patients must have fasting serum glucose < 125 mg/dL (6.9 mmol/L), and hemoglobin A1C <= 6%.

Exclusion criteria

Patients must not have an uncontrolled intercurrent illness, leptomeningeal disease, or active infection requiring parenteral therapy.

Study design

Design

Study phase: 2

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):	23-01-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cisplatin
Generic name:	N/A
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cixutumumab
Generic name:	N/A
Product type:	Medicine
Brand name:	Pemetrexed
Generic name:	ALIMTA
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-04-2011
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	04-05-2011
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-05-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-06-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-07-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-11-2011
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-04-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-06-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	31-07-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-11-2012
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-12-2012
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
EudraCT	EUCTR2010-024014-60-NL
ClinicalTrials.gov	NCT01232452
CCMO	NL34880.028.11