A PHASE II, DOUBLE-BLIND, PLACEBO CONTROLLED, RANDOMIZED STUDY EVALUATING THE SAFETY AND EFFICACY OF CARBOPLATIN/PACLITAXEL AND CARBOPLATIN/PACLITAXEL/BEVACIZUMAB WITH AND WITHOUT GDC-0941 IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED OR RECURRENT NON-SMALL CELL LUNG CANCER.

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PRIMARY OBJECTIVES Part I - To evaluate the efficacy (as measured by PFS) of GDC-0941 340 mg +carboplatin * paclitaxel (Arm A) versus carboplatin * paclitaxel (Arm B) in all patients with squamous NSCLC -To evaluate the efficacy (as measured by PFS...

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

Summary

ID

NL-OMON39705

Source
ToetsingOnline

Brief title
Genentech GO27912

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Previously untreated advanced or recurrent non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Genentech Inc.
Source(s) of monetary or material Support: Farmaceutical Industry

Intervention

Keyword: GDC-0941, Non-small cell lung cancer

Outcome measures

Primary outcome

Primary Efficacy Outcome Measure

For ALL Arms and all predefined study populations (see Section 3.3.5), the

primary efficacy outcome measure is:

• PFS, defined as the time from randomization to disease progression as

assessed by the investigator per RECIST v1.1 or death from any cause on study

(<= 30 days after the last dose of study treatment) whichever occurs first

Secondary outcome

Secondary Efficacy Outcome Measures

For ALL Arms and all predefined study populations (see Section 3.3.5), the

secondary efficacy outcome measures are:

• Objective tumor response as assessed by the investigator using RECIST v1.1; objective responses must be confirmed >= 28 days after initial response

• Duration of objective response, defined as the time from first observation of an objective tumor response until first observation of disease progression as assessed by the investigator using RECIST v1.1

• OS, defined as the time from randomization until death from any cause

Safety Outcome Measures

The safety and tolerability of GDC-0941 in combination with carboplatin + paclitaxel with or without bevacizumab will be assessed using the following outcome measures:

• Incidence, nature, and severity of adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0

• Clinically significant changes in vital signs, physical findings, and clinical laboratory results during and following administration of GDC-0941

Pharmacokinetic Outcome Measures

The pharmacokinetic outcome measures are the following:

• PK parameters (e.g., Cmax and Cmin) of GDC-0941, paclitaxel, 6-α-OH-paclitaxel and carboplatin

Study description

Background summary

On the basis of preliminary Phase Ib data from Study GDC4628g, the safety profile for GDC 0941, carboplatin, and paclitaxel with or without bevacizumab appears to be similar to the safety profile of these standard-of-care regimens without GDC-0941. This randomized Phase II study will provide a better understanding of the differences in the severity and rate of AEs of these regimens with and without GDC-0941. In order to detect clinically significant differences in safety profiles early, an Internal Monitoring Committee (IMC; see Section 3.4.6.2 for details) will convene on at least two occasions to review all available safety data and make the recommendation to either continue the study without changes to the protocol, modify the safety monitoring and/or eligibility criteria of the protocol, add additional safety reviews to address emerging safety issues, or to terminate parts of the study or the entire study. Please refer to page 14 of the protocol dated 25 July 2011 for more information.

Study objective

PRIMARY OBJECTIVES

Part I
- To evaluate the efficacy (as measured by PFS) of GDC-0941 340 mg +carboplatin * paclitaxel (Arm A) versus carboplatin * paclitaxel (Arm B) in all patients with squamous NSCLC
-To evaluate the efficacy (as measured by PFS) of GDC-0941 340 mg +carboplatin * paclitaxel (Arm A) versus carboplatin * paclitaxel (Arm B) in patients with squamous NSCLC with PIK3CA amplification
- To evaluate the efficacy (as measured by PFS) of GDC-0941 340 mg + carboplatin * paclitaxel * bevacizumab (Arm C) versus carboplatin * paclitaxel * bevacizumab (Arm D) in all patients with non-squamous NSCLC
- To evaluate the efficacy (as measured by PFS) of GDC-0941 340 mg + carboplatin * paclitaxel * bevacizumab (Arm C) versus carboplatin * paclitaxel **bevacizumab (Arm D) in patients with non-squamous NSCLC with PTEN-loss status

Part II
- To evaluate the efficacy (as measured by PFS) of GDC-0941 260 mg + carboplatin * paclitaxel * bevacizumab (Arm E) versus carboplatin* paclitaxel * bevacizumab (Arm F) in all patients with non-squamous NSCLC

SECONDARY OBJECTIVES

Part I
- To assess the clinical activity (as measured by ORR, duration of response and OS), of GDC-0941 340 mg + carboplatin * paclitaxel (Arm A) versus carboplatin * paclitaxel (Arm B) in all patients with squamous NSCLC and in patients with squamous NSCLC with PIK3CA amplification
- *To evaluate the safety and tolerability of GDC-0941 340 mg when combined with carboplatin * paclitaxel in all patients with squamous NSCLC
- To assess the clinical activity (as measured by ORR, duration of response and OS), of GDC-0941 340 mg + carboplatin * paclitaxel * bevacizumab (Arm C) versus carboplatin * paclitaxel * bevacizumab (Arm D) in all patients with non-squamous NSCLC and in patients with non-squamous NSCLC with PTEN-low status
- To evaluate the safety and tolerability of GDC-0941 340 mg when combined with carboplatin * paclitaxel + bevacizumab in all patients with non-squamous NSCLC

Part II
- To assess the clinical activity (as measured by ORR, duration of response and OS), of GDC-0941 260 mg + carboplatin* paclitaxel * bevacizumab (Arm E) versus carboplatin * paclitaxel * bevacizumab (Arm F) in all patients with non-squamous NSCLC
- To evaluate the safety and tolerability of GDC-0941 260 mg when combined with carboplatin * paclitaxel + bevacizumab in all patients with non-squamous NSCLC

Part I and Part II
- To assess PK parameters (e.g., Cmax and Cmin) of GDC-0941, paclitaxel, and carboplatin when administered in combination to patients with squamous or non-squamous NSCLC
- *To assess the prevalence of PIK3CA amplification and PTEN-loss/low status in tumor samples from patients with squamous or non-squamous NSCLC
- To assess the prognostic effects of PIK3CA amplification and PTEN-loss/low status on PFS in patients with squamous or non-squamous NSCLC

EXPLORATORY OBJECTIVES
The exploratory objectives of this trial (squamous and non-squamous NSCLC) are:

Part I and Part II
- To explore the prevalence of oncogenic alterations of EGFR, KRAS, LKB1, MET and other potential biomarkers in archival tumor (or new biopsy, if archival tissue is not available), circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and/or tumor DNA in urine
- To explore the value of oncogenic alterations of EGFR, KRAS, LKB1, MET, and other potential biomarkers in archival tumor (or new biopsy, if archival tissue is not available), CTCs, ctDNA and/or tumor DNA in urine as predictors of response to GDC-0941 + carboplatin * paclitaxel with or without bevacizumab compared with standard of care without GDC-0941
- To measure the number of CTCs and levels of cancer-associated proteins in blood, and assess their value as predictors of response to GDC-0941 +

carboplatin * paclitaxel with or without bevacizumab compared with standard of care without GDC-0941
- To explore predictors of response to GDC-0941 + carboplatin * paclitaxel with or without bevacizumab compared with standard of care without GDC-0941 based on exploratory analyses using molecular data obtained from tumor tissue by exon resequencing, mRNA and/or miRNA expression profiling and/or DNA copy number profiling
- To assess the potential relationship between concentration of GDC-0941, paclitaxel and carboplatin and tumor response and/or safety
- To explore the relationship between pharmacogenetic differences in drug-metabolizing enzymes and transporters and other patient-specific covariates with pharmacokinetics and pharmacodynamics of GDC-0941 when administered in combination with carboplatin * paclitaxel with or without bevacizumab
- To evaluate the efficacy (as measured by PFS, OS, and objective response rate) of GDC-0941 260 mg + carboplatin * paclitaxel * bevacizumab (Arm E) versus carboplatin* paclitaxel * bevacizumab in both Arms D and F, in the non-squamous NSCLC overall patient group and in patients with PTEN-low status, if data in Arm D and F are suitable for pooling
- To evaluate the efficacy (as measured by PFS and OS) of GDC-0941 260 mg + Carboplatin * paclitaxel * bevacizumab (Arm E) and GDC-0941 340 mg + carboplatin * paclitaxel * bevacizumab (Arm C) versus carboplatin* paclitaxel * bevacizumab in both Arms D and F, in the non-squamous NSCLC overall patient group and in patients with PTEN-low status, if data in Arms D and F are suitable for pooling, and data in Arms C and E are suitable for pooling as well

Study design

This is a Phase II, multicenter, randomized, double-blind, placebo-controlled trial with six arms that will be conducted at approximately 90 to 120 sites in countries of the European Union (EU), the United States (US), and other select countries.

Part I
Arms A and B are designed to evaluate the efficacy, safety, and pharmacokinetics of GDC-0941 340 mg when combined with carboplatin + paclitaxel in patients with previously untreated advanced or recurrent squamous NSCLC (Stage IV).
• Arm A: GDC-0941 340 mg + carboplatin + paclitaxel
• Arm B: Placebo (corresponding to GDC-0941 340 mg) + carboplatin + paclitaxel
Patients will be randomly assigned to Arm A versus Arm B in 1:1 ration using the following predefined stratification variables: performance status (ECOG performance status 0 versus 1) and smoking status (former/never versus current).
Arms C and D are designed to evaluate the efficacy, safety, and pharmacokinetics of GDC-0941 340 mg when combined with carboplatin * paclitaxel * bevacizumab in previously untreated patients with advanced or

recurrent non-squamous NSCLC (Stage IV).
• Arm C: GDC-0941 340 mg + carboplatin + paclitaxel * bevacizumab
• Arm D: Placebo (corresponding to GDC-0941 340 mg) + carboplatin + paclitaxel * bevacizumab

Patients will be randomly assigned to Arm C versus Arm D in a 1:1 ratio using the following predefined stratification variables: performance status (ECOG performance status 0 versus 1) and smoking status (former/never versus current).

Part II

Part II is designed to evaluate the efficacy, safety, and pharmacokinetics of GDC-0941 260 mg
when combined with carboplatin * paclitaxel * bevacizumab in previously untreated patients
with advanced or recurrent non-squamous NSCLC (Stage IV).

• Arm E: GDC-0941 260 mg + carboplatin + paclitaxel * bevacizumab
• Arm F: Placebo (corresponding to GDC-0941 260 mg) + carboplatin + paclitaxel * bevacizumab

Patients will be randomly assigned to Arm E versus Arm F at a 2:1 ratio using the following
predefined stratification variables: performance status (ECOG performance status 0 versus 1)and smoking status (former/never versus current).

Arms E and F may open enrollment to patients with non-squamous NSCLC only after Arms C and D have completed enrollment. This sequential enrollment plan will avoid complications from changing the non-squamous randomization scheme from 1:1 in Arms C
and D to 2:1 in Arms E and F.

In all arms, study treatment will be given in cycles repeated every 21 days. Patients will receive paclitaxel (200 mg/m2), administered IV on Day 1, and carboplatin (AUC of 6 mg/mL • min by the Calvert formula), administered IV on Day 1, for a total of 4 cycles. Patients in Arms C, D, E and F will also receive bevacizumab (15 mg/kg), administered IV on Day 1 of each cycle for a maximum of 24 months (34 cycles).

During the first 4 cycles with carboplatin + paclitaxel with or without bevacizumab, patients will receive GDC-0941 at 340 mg by mouth (Arms A and C; in tablet formulation , GDC-0941 at 260 mg by mouth (Arm E; in tablet formulation, see Sections 3.2.1 and 4.3.1), or placebo (corresponding to either to GDC-0941 340 mg or GDC-0941 260 mg)or placebo by mouth (Arms B, D and F) once daily on Days 1*14 of every 21-day cycle. Starting with Cycle 5, all patients will receive GDC-0941 or placebo once daily continuously. In the case

of Arms C, D, E and F, GDC-0941/placebo will be given with bevacizumab.

Patients in Arms B, D and F with progression NSCLC may cross over to Arms A, C or E, respectively, during the first 4 cycles with carboplatin + paclitaxel with or without bevacizumab or after chemotherapy has been completed (Cycle >= 5).

Intervention

Subjects will receive GDC-0941 or placebo in combination with carboplatin and paclitaxel with or without bevacizumab.
GDC-0941/placebo tablets are administered once daily beginning on Day 1 of Cycle 1 until disease progression or intolerable toxicity. For the first 4 cycles, GDC-0941/placebo will be taken for the first 14 days of each 21-day cycle. Starting with Cycle 5, GDC-0941/placebo will be taken once daily continuously.

Study burden and risks

On the basis of a maximum participation of 26 months (max. 34 cycles of 3 weeks) (see appendix A of protocol) a subject undergoes the following procedures:
38x vitals signs
38x oxygen measurement on fingertip
1x length
36x weight
38x physical exam
17x ECG
19x CT/MRI
38x blood draw
1x pregnancy test
1x urine sample (arm A&B)
36x urine sample (arm C&D)
1x biopsy (or archival sample)
4x i.v. infusion with paclitaxel and carboplatin
34x i.v. infusion with bevacizumab
714 days GDC-0941/placebo-tablets intake

The most frequent and most severe side effects observed in patients treated with GDC 0941 are:
• Common side effects (occurring in at least 10 out of 100 patients), but may be of severe intensity: fatigue, nausea, diarrhea and rash.
• Common side effects (occurring in at least 10 out of 100 patients) of mild to moderate intensity are: dysgeusia (abnormal sense of taste), vomiting, decreased appetite and pruritus (itchiness), redness of lips and the lining of mouth.

Information about less common side-effects of GDC-0941 and about the side-effects and risks of the other study medications and procedures are described in Addendum V of the Patient Information Leaflet.

Contacts

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For ALL Arms:
• All patients must consent to the collection of an archival formalin-fixed paraffin embedded (FFPE) block or freshly cut unstained tumor slides from archival tumor tissue (10-15 preferred, minimum of 5 slides required) or a newly collected tumor sample for PIK3CA amplification testing and/or PTEN IHC, as well as for other protocol-mandated exploratory assessments.
• Age >= 18 years

• ECOG performance status of 0 or 1
• Disease that is measurable per RECIST v1.1
• Adequate hematologic and end organ function, defined by specific laboratory results obtained within 14 days prior to the first study treatment.;For Arms A and B:
• Histologically documented advanced (Stage IV) or recurrent squamous NSCLC;For Arms C, D, E & F:
• Histologically documented advanced (Stage IV) or recurrent non-squamous NSCLC

Exclusion criteria

For ALL Arms:
• NSCLC with documented EGFR mutation assosciated with response to EGFR inhibitors or documented fusion gene involving the anaplastic lymphoma kinase (ALK) gene (such as EML4-ALK)
• Prior therapy (including chemotherapy, antibody therapy, tyrosine kinase inhibitors, radiotherapy, immunotherapy, hormonal therapy, or investigational therapy) before Day 1 of Cycle 1 for the treatment of advanced (Stage IV) or recurrent NSCLC
• Evidence of tumor invading major blood vessels on imaging
• Known CNS disease except for treated brain metastases
• Leptomeningeal disease
• Malignancies other than NSCLC successfully treated within 3 years prior to randomization, except for adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent and carcinoma in situ of any anatomic location treated with curative intent
• Type I diabetes
• Type II diabetes requiring chronic therapy with insulin
• Requirement for supplemental oxygen therapy to perform activities of daily living
• Unstable angina
• Serious cardiac arrhythmia requiring medication during the study
• New York Heart Association (NYHA) Class II or greater congestive heart failure
• History of malabsorption syndrome or other condition that would interfere with enteral absorption
• Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 of Cycle 1, or anticipation of need for major surgical procedure during the course of the study
• Clinically significant history of liver disease, including cirrhosis, active viral hepatitis and current alcohol abuse
• Known HIV infection
• Active infection requiring IV antibiotics
• Active inflammatory diseases that require immunosuppressants, including small or large intestine inflammation such as Crohn*s disease or ulcerative colitis.
• Patients currently receiving immunosuppressants (e.g. sulfasalazines) are considered to have disease and are therefore ineligible
• Active autoimmune disease that is not controlled by nonsteroidal anti inflammatory drugs
• Need for current chronic corticosteroid therapy (>=10 mg of prednisone per day or an

equivalent dose of other anti inflammatory corticosteroids)
• Uncontrolled hypercalcemia, defined as values above the ULN, despite optimal management including bisphosphonate therapy
• Uncontrolled hypomagnesemia or hypokalemia, defined as values below the LLN despite optimal electrolyte supplementation or management
• Grade >= 2 peripheral neuropathy;Bevacizumab-Specific Exclusion Criteria for Arms C, D E and F:
• Histologically or cytologically documented, advanced, mixed non*small cell and small cell tumors or mixed adenosquamous carcinomas with a predominant squamous component
• Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg)
• Prior history of hypertensive crisis or hypertensive encephalopathy
• History of myocardial infarction within 6 months prior to Day 1 of Cycle 1
• History of stroke or transient ischemic attacks (TIAs) within 6 months prior to Day 1 of Cycle 1
• Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1
• History of hemoptysis defined as bright red blood of >=1/2 teaspoon within 1 month prior to Day 1 of Cycle 1
• Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
• Minor surgery, including insertion of an indwelling catheter, within 48 hours prior to Day 1 of Cycle 1
• History of abdominal fistula, GI perforation, or intra-abdominal abscess within 6 months prior to Day 1 of Cycle 1
• Patients diagnosed with a tracheo-esophageal fistula
• Serious, non-healing wound, active ulcer, or untreated bone fracture
• Proteinuria, as demonstrated by >= 2.0 g of protein in a 24 hour collection

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):	17-06-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	GDC-0941
Generic name:	n.v.t.
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-02-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-07-2012
Application type:	First submission
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)
Approved WMO Date:	29-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-03-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-05-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	01-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-10-2015
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
EudraCT	EUCTR2011-002893-21-NL
ClinicalTrials.gov	NCT01493843
CCMO	NL39462.042.12