A PHASE 3 RANDOMIZED, DOUBLE-BLIND STUDY OF PF-06439535 PLUS PACLITAXEL-CARBOPLATIN AND BEVACIZUMAB PLUS PACLITAXEL-CARBOPLATIN FOR THE FIRST-LINE TREATMENT OF PATIENTS WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

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Primary Objective* The primary objective of this study is to compare the confirmed objective response rate (ORR) by Week 19 following treatment with bevacizumab-Pfizer in combination with paclitaxel and carboplatin to bevacizumab-EU plus paclitaxel...

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

Summary

ID

NL-OMON45020

Source
ToetsingOnline

Brief title
9002/0328 (B7391003)

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER - certain type of lungcancer

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: the Sponsor (Pfizer Inc.)

Intervention

Keyword: Bevacizumab, Biosimilar, NSCLC, phase 3

Outcome measures

Primary outcome

* Objective Response Rate (ORR), evaluating the best response achieved by Week 19 and subsequently confirmed by 6 weeks thereafter, in accordance with Response Evaluations Criteria in Solid Tumors (RECIST) version 1.1.

Secondary outcome

* Safety characterized by type, incidence, severity, timing, seriousness, and relationship to study therapy of adverse events, including cardiotoxicity and infusion-related reactions, and laboratory abnormalities at 1 year from randomization;

* Duration of response (DOR), 1 year progression-free survival (PFS) rate at 1-year survival rate from randomization;

* Peak and trough bevacizumab-Pfizer and bevacizumab-EU concentrations at selected cycles up to 1 year from randomization;

* Incidence of anti-drug (bevacizumab) antibodies (ADA), including neutralizing

antibodies (NAb) up to 1 year from randomization;

Study description

Background summary

Background
Biological therapeutics are large complex protein molecules that require a wide variety of analytical methods to ensure consistent quality. As a result of their complexity and manufacturing methods, biologic products have inherent variability and the development of an exact replicate is not possible. Biosimilars are structurally highly similar version of marketed biological medicines that are supported by appropriate analytical testing and clinical trials to demonstrate that they are sufficiently *similar* (both in structure and clinical function) to the marketed biological product.

Development as a biosimilar requires head-to-head comparison to an approved reference product. The European Union (EU) has a legal basis for approval of biosimilars, which defines a reference product as a product authorized in the EU (bevacizumab-EU). Similarly, the United States Biologics Price Competition and Innovation Act created an abbreviated approval pathway for biological products that are demonstrated to be biosimilar with a Food and Drug Administration (FDA)-licensed biological product (bevacizumab-US).

BEVACIZUMAB
Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors; Flt-1 and kinase insert domain receptor (KDR), on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis.1,2 The blockade interaction of VEGF by bevacizumab inhibits angiogenesis and tumor growth. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

Study objective

Primary Objective

* The primary objective of this study is to compare the confirmed objective response rate (ORR) by Week 19 following treatment with bevacizumab-Pfizer in combination with paclitaxel and carboplatin to bevacizumab-EU plus paclitaxel and carboplatin in patients who have not received previous treatment for

advanced non-squamous
non-small cell lung cancer (NSCLC).

SECONDARY OBJECTIVES

* To evaluate the safety of bevacizumab-Pfizer plus paclitaxel and carboplatin and bevacizumab-EU plus paclitaxel and carboplatin;

* To evaluate secondary measures of tumor control;

* To evaluate the population pharmacokinetics (PK) of bevacizumab-Pfizer and bevacizumab-EU;

* To evaluate the immunogenicity of bevacizumab-Pfizer and bevacizumab-EU.

Study design

This is a multinational, double-blind, randomized, parallel-group Phase 3 clinical trial evaluating the efficacy and safety of bevacizumab-Pfizer plus paclitaxel and carboplatin versus bevacizumab-EU plus paclitaxel and carboplatin in first-line treatment for patients with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

Approximately 355 patients will be enrolled in each treatment arm for a total of approximately 710 patients at over 300 centers. Patients will be randomized (1:1) to receive either treatment of bevacizumab-Pfizer plus paclitaxel and carboplatin or bevacizumab-EU plus paclitaxel and carboplatin. Randomization will be stratified by region (according to the location of the drug depot supplying the site), sex (male/female) and smoking history (never/ever).
Patients will participate in the study on average for approximately 13 months. This includes about 1 month of screening and at least 1 year for treatment and follow-up.
Actual length of participation for individual patients will depend upon the actual duration of treatment. Minimum expected participation is 1 year unless shorter due to death, withdrawal of consent, or early termination of the trial.

Following the completion of at least 4 but no more than 6 cycles of chemotherapy, or upon discontinuation of chemotherapy, patients on either bevacizumab-Pfizer or bevacizumab-EU can continue to receive bevacizumab monotherapy with blinded drug product every 3 weeks, until disease progression or unacceptable toxicity. Study treatment with bevacizumab is to continue until disease progression, as assessed by RECIST 1.1, in the judgment of the investigator. Thus, treatment of individual patients with bevacizumab beyond Week 19 of the study is expected as appropriate for individual patients.
Patients experiencing disease progression are to discontinue study treatment and begin the follow-up phase of the trial.
Patients who discontinue study treatment for reasons other than disease

progression, withdrawal of consent, or the start of new anticancer therapy prior to Week 19 are to have tumor assessments according to the protocol schedule through Week 19. If the investigator identifies a complete or a partial response based on RECIST 1.1 criteria, those responses should be confirmed after 6 weeks, whenever possible, with the same imaging sequence.

Two one-sided hypothesis tests will be carried out in the study for ORR in order to show that bevacizumab-Pfizer is equivalent to bevacizumab-EU. For the EU equivalence will be considered established if the 95% confidence interval of the risk ratio falls into the margins of
0.73 to 1.37.

Safety will be reviewed throughout the trial in a blinded manner by the study team and in an unblinded manner by an external Data Monitoring Committee (EDMC).

Intervention

Day 1 of a 21-day cycle for each of at least 4 and no more than six (6) 21-day cycles. Once paclitaxel and carboplatin have been stopped, treatment with bevacizumab-Pfizer or
bevacizumab-EU is continued every 3 weeks (monotherapy) until unacceptable toxicity, regulatory request, death, at the request of the investigator, patient discontinuation, or progression of disease.

Study burden and risks

Any research has some risks, which may include things that could make you sick, make you feel uncomfortable, or harm you.
The most frequent side effects of bevacizumab * EU are: high blood pressure. Numbness or tingling in hands or feet, deviations (decreases) in blood cell count, weakness, lack of energy, tiredness, diarrhea, nausea and vomiting.

You can read more about the side effects of bevacizumab * EU and the other used medications for this treatment in Appendix 3: 'Risks and Side Effects'. In this appendix information is also given on less frequent side effects and possible side effects due to the procedures that are part of the study.

Contacts

Public
Pfizer

East 42nd Street 235

New York NY 10017
US
Scientific
Pfizer

East 42nd Street 235
New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male and female patients age * 18 years of age, or * age of consent in the region.;2. Newly diagnosed Stage IIIB or IV non-small cell lung cancer (according to Revised International System for Staging Lung Cancer criteria of 2010) or recurrent non-small cell lung cancer (NSCLC).;3. Histologically or cytologically confirmed diagnosis of predominately non-squamous NSCLC.;4. At least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1).;5. For patients with recurrent disease, at least 6 months must have elapsed since completing adjuvant or neoadjuvant treatment.;6. Screening scan (computed tomography [CT] or magnetic resonance imaging [MRI]) of the head, chest, abdomen (with adrenal glands), and other disease sites, as clinically indicated, to assess disease burden.;7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.;8. Screening laboratory values within the following limits (where deviation of up to 10% is acceptable for any single value if in the investigator*s opinion the patient does not have an increased safety risk):;Bone Marrow Function;a. Absolute neutrophil count (ANC) *1.5 x 109 cells/L (1500/mm3);
b. Platelet count *100 x 109 cells/L (100,000/mm3);
c. Hemoglobin *9.0 g/dL (90 g/L); Renal Function
d. Serum or plasma creatinine *1.5 x upper limit of normal (ULN);;e. Urine dipstick proteinuria <2+ (ie, either 0, trace, or 1+). If urine dipstick is
>1+ then a 24 hour urine for protein must have demonstrated urinary excretion of

*500 mg of protein per day, or urine protein to creatinine ratio (UPC) ratio <1;;Liver Function;f. Total bilirubin *1.5 x ULN (<3 ULN if Gilbert*s disease);;g. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)
*3 x ULN (*5 x ULN if liver metastases are present).;9. Recovery (to Grade 1 or baseline) from all clinically significant adverse effects of prior therapies (excluding alopecia).;10. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.;11. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.;12. Be eligible to receive study treatment of bevacizumab, paclitaxel, and carboplatin based on local standard of care, for the treatment of advanced or metastatic non-squamous NSCLC.;13. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and for at least 6 months after the receipt of the last dose of assigned study treatment.;Female patients who are not of childbearing potential (ie, meet at least 1 of the following criteria):;* Have undergone a documented hysterectomy and/or bilateral oophorectomy;;* Have medically confirmed ovarian failure; or;* Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.;All other female patients, (including females with tubal ligations) will be considered to be of childbearing potential.

Exclusion criteria

1. Small cell lung cancer (SCLC) or combination SCLC and NSCLC. Squamous-cell tumors and mixed adenosquamous carcinomas of predominantly squamous nature.;2. Evidence of a tumor that compresses or invades major blood vessels or tumor cavitation that is likely to bleed.;3. Known sensitizing EGFR mutations (for example, deletion 19 or L858R) or EML4-ALK translocation positive mutations.If mutation testing is performed, results must be reviewed and confirmed as negative for mutations prior to randomization.;4. History of other cancer within 5 years prior to screening for this study, with the exception of adequately treated ductal carcinoma in situ of the breast, cervical carcinoma in situ, or basal or squamous cell skin cancer.;5. Prior systemic therapy for NSCLC; prior neoadjuvant /adjuvant therapy is allowed if surgical resection for primary disease was performed.;6. History of local radiation for painful bone metastases in the last 2 weeks. (Patients with bone metastases are eligible, however those with symptomatic or painful bone metastases should not have received palliative local radiation for at least 2 weeks prior to randomization).;7. History of hemoptysis (>2.5 mL per event) in the last 3 months or severe bleeding. Evidence of current thrombotic or bleeding disorders. Therapeutic anticoagulation and/or coagulation abnormalities (eg, INR >1.5 and aPTT greater than ULN unless on prophylactic anticoagulation).;8. Medically uncontrolled hypertension or systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg.;9. Peripheral motor or sensory neuropathy with value of * grade 2.;10. Major surgery, or any investigational agents, within 4 weeks before the administration of the first dose of study treatment. Planned major surgery during the treatment period.;11. Any unhealed wound or bone fracture.;12. Active infection. Patients must be off anti-infective

agents.;13. Comorbities that would increase the risk of toxicity.;14. Concurrent administration of other anticancer therapies. Bisphosphonate or Rank-Ligand inhibitor therapy for pre-existing bone metastases or osteoporosis is allowed.;15. Known central nervous system (CNS) metastases, as evidenced by appropriate scans, clinical symptoms, cerebral edema, and/or progressive growth (if a suspected CNS lesion is not confirmed by pathology).Treated and stable (asymptomatic; off steroids) brain metastases are allowed.;16. Active uncontrolled cardiac disease, such as cardiomyopathy, congestive heart failure (CHF) New York Heart Association (NYHA) functional classification of *3, unstable angina, or myocardial infarction within 12 months before first dose of study treatment. Clinically significant cardiovascular disease, peripheral vascular disease, transient ischemic attack, cerebrovascular accident.;17. History of severe hypersensitivity reaction to any of the products to be administered during the study, including mammalian cell derived drug products, taxanes, bevacizumab, murine proteins, or excipients in their formulations.;18. Clinical contraindication to treatment with steroids preventing use as part of paclitaxel premedication.;19. Pregnant female patients; breastfeeding female patients; male patients with partners currently pregnant; patients able to father children and female patients of childbearing potential who are unwilling or unable to use 2 highly effective methods of contraception as outlined in this protocol for the duration of the study, and for at least 6 months after the receipt of the last dose of study treatment. ;Note: For female patients of childbearing potential, to exclude the possibility of pregnancy, a serum or urine pregnancy test with sensitivity of at least 25 mIU/mL will be performed on 2 occasions by the local certified laboratory, and 2 negative tests are required before receiving the first dose of investigational product. The second negative test should be done during the first 5 days of the menstrual period, immediately preceding the first dose of any study treatment. In the absence of regular menstrual bleeding, the patient should have used 2 different methods of contraception for at least 1 month before the second pregnancy test. A patient is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active. This includes women who are using contraceptives or whose sexual partners are either sterile or using contraceptives.;Please see the protocol for exclusion criterias 20-25.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-10-2015
Enrollment:	20
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:	bevacizumab
Generic name:	bevacizumab

Ethics review

Approved WMO

Date:	05-03-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	26-06-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	06-10-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	21-10-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-12-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2014-003878-16-NL
CCMO	NL52220.056.15