Multicenter, randomized, double-blind, phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard pemetrexed therapy compared to placebo plus standard pemetrexed therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy

Published: 21-11-2008
Last updated: 06-05-2024

To investigate the efficacy and safety of BIBF 1120 as compared to placebo in patients with stage IIIB/IV or recurrent non small cell lung cancer treated with standard therapy of pemetrexed after failure of first line chemotherapy.

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

Summary

ID

NL-OMON36930

Source
ToetsingOnline

Brief title
BIBF plus Pemetrexed in 2nd line NSCLC patients

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: BIBF 1120, non small cell lung cancer

Outcome measures

Primary outcome

Progression free survival (imaging assessed by an independent central review according to the modified RECIST criteria)

Secondary outcome

* Overall survival (key secondary endpoint)

* Tumor response according to the modified RECIST criteria (objective tumor response, disease control, duration of disease control)

* Incidence and intensity of adverse events according to the common terminology criteria for adverse events (CTCAE version 3.0)

* Clinical improvement

* Changes in safety laboratory parameters

* Quality of life measured by standardized questionnaires (EQ-5D, EORTC QLQ C-30, EORTC QLQ LC 13)

* Pharmacokinetics of BIBF 1120 (and of clinical relevant metabolites, if feasible)

Study description

Background summary

Patients with locally advanced and/or metastatic non small cell lung cancer (NSCLC) are generally treated with a platinum combination in first-line setting. Despite responses and transient regression of the tumor, most of the patients will relapse and their tumors start to grow and metastasize. New drugs and/or therapy regimens are needed to prolong life and ameliorate signs and symptoms of NSCLC in these patients. BIBF 1120 is a potent, orally available triple kinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs. Phase I dose selection studies revealed that BIBF 1120 is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (nausea, diarrhea, vomiting, abdominal pain) and reversible elevations of liver enzymes. Initial signs of clinical activity are shown, including an encouraging rate of patients with stabilization of their tumor.

Treatment with BIBF 1120 of patients with locally advanced and/or metastatic NSCLC, who previously had failed up to two lines of prior chemotherapy, suggests clinical efficacy of BIBF 1120.

Since therapy with one drug only does not appear to yield a satisfactory outcome, further treatment options combining various therapeutic principles should be evaluated to improve therapy of patients with locally advanced and/or metastatic NSCLC who have failed one line of prior chemotherapy.

The present trial will investigate the efficacy and safety of BIBF 1120 in combination with standard therapy pemetrexed as compared to placebo plus standard pemetrexed in patients with locally advanced and/or metastatic NSCLC (Stage IIIB/IV) who have failed first line chemotherapy. See for more information page 18-19 of the study protocol.

Study objective

To investigate the efficacy and safety of BIBF 1120 as compared to placebo in patients with stage IIIB/IV or recurrent non small cell lung cancer treated with standard therapy of pemetrexed after failure of first line chemotherapy.

Study design

A multicentre, randomized, double-blind, placebo-controlled, parallel-group comparison of BIBF 1120 plus standard pemetrexed therapy compared to placebo plus standard pemetrexed therapy in patients with stage IIIB/IV or recurrent non small cell lung cancer after failure of first line chemotherapy.

After giving informed consent patients who fulfil all the inclusion and exclusion criteria will be randomized into 2 equal sized groups of both max. 650 patients.

One group will receive standard dose pemetrexed (500 mg/m2 intravenously) on Day 1 with BIBF 1120 (200 mg orally twice daily) on Days 2-21 of each 3 week cycle. The other group will receive standard dose pemetrexed on Day 1 plus placebo twice daily on Days 2-21 of each 21 day cycle.

Patients will receive adequate pre- and concomitant medication required for pemetrexed administration. Patients will be treated with combination therapy until unacceptable toxicity, progression of neoplastic disease or another of the withdrawal criteria mentioned in Section 6.3 is met.

Intervention

One group will receive standard dose pemetrexed (500 mg/m2 intravenously) on Day 1 with BIBF 1120 (200 mg orally twice daily) on Days 2-21 of each 3 week cycle. The other group will receive standard dose pemetrexed on Day 1 plus placebo twice daily on Days 2-21 of each 21 day cycle.

Study burden and risks

Risks of BIBF 1120:
side effects reported in more than 10 % of patients:increased liver function tests, diarrhea, loss of appetite, nausea, vomiting, abdominal pain and tiredness. These side effects were usually reversible.
side effects which occurred in 1 to 10 % of patients:
dry mouth, taste changes, indigestion, flatulence (gas), dizziness, headache, high blood pressure, low white blood cell count), constipation, bone and liver pain, muscle cramps, chest pain, back pain, tumor pain and infections including those in the urine, chest and sinuses, itching, rash, hair loss, dry skin, sweating, chills, fever, coughing up small amounts of blood, abnormal skin sensations.
occurring in less than 1 % of patients:
nose dryness, yellowing of the skin due to raised bilirubin in the blood (jaundice), skin or mouth pain, muscle pain, joint pain or swelling, skin swelling, groin pain, breast pain, memory impairment or change in attention, tremor, abnormal heat beats, fast or slow heart beats, low blood sugar or low blood potassium, changes in kidney function, eye redness, cough, bladder infection, pneumonia, bleeding, bleeding into the brain and death.
It is possible that BIBF 1120 in combination with natural sunlight or artificial sunlight (UV radiation) may cause harmful effects to skin or eye.

Risks of pemetrexed:
reported in more than 10 % of patients:

low red blood cell count, tiredness, weakness, fever, swelling in feet, loss of appetite, nausea, constipation, vomiting, diarrhea, mouth, throat and/or lip sores, shortness of breath, chest pain, muscle pain, nerve pain in hands and/or feet, increased chance of infection, hair loss, rash, change in mood and/or depression.

side effects reported in 1 to 10 % of patients:
low white blood cell count, low platelet count, decreased kidney function, increased liver function tests, joint pain, difficulty swallowing and/or swelling of the tube that goes from the mouth to the stomach, blood clots in legs or lungs, infection with fever, allergic reaction and dehydration.

The rare risks and side effects are inflammation of the large intestine with diarrhea, inflammation at the site of previous radiation therapy.

Risks of pemetrexed plus BIBF
In a small trial investigating the effects of combined pemetrexed and BIBF 1120 treatment (12 patients) more than 10% experienced the following side effects: fatigue, nausea, loss of appetite, rash, diarrhea, vomiting, abdominal pain, liver enzyme elevations in the blood, change in taste, itching, and difficulty sleeping.

Please see section E9 of this form for risks on blood draws, ECG, CT scan, MRI and bone scan.

Contacts

Public
Boehringer Ingelheim

Binger Str. 173
55216 Ingelheim
NL
Scientific
Boehringer Ingelheim

Binger Str. 173
55216 Ingelheim
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* Male or female patient aged 18 years or older
* Histologically or cytologically confirmed Stage IIIB, IV (according to AJCC) or recurrent NSCLC (non squamous histologies)
* Relapse or failure of one first line chemotherapy (in the case of recurrent disease one additional prior regimen is allowed for adjuvant, neoadjuvant or neoadjuvant plus adjuvant therapy)
* At least one target tumor lesion that has not been irradiated within the past three months and that can accurately be measured by magnetic resonance imaging (MRI) or computed tomography (CT) in at least one dimension (longest diameter to be recorded) as *20 mm with conventional techniques or as *10 mm with spiral CT
* Life expectancy of at least three months
* ECOG score of 0 or 1
* Patient has given written informed consent which must be consistent with the International Conference on Harmonization * Good Clinical Practice (ICH-GCP) and local legislation

Exclusion criteria

* More than one prior chemotherapy regimen for advanced, metastatic or recurrent NSCLC
* More than one chemotherapy treatment regimen (either neoadjuvant or adjuvant or neoadjuvant plus adjuvant) prior to first line chemotherapy of advanced, metastatic or recurrent NSCLC
* Previous therapy with other vegfr inhibitors (other than bevacizumab) or pemetrexed for treatment of nsclc
* Persistence of clinically relevant therapy related toxicities from previous chemotherapy and/or radiotherapy
* Treatment with other investigational drugs or treatment in another clinical trial within the past four weeks before start of therapy or concomitantly with this trial
* Chemo-, hormone-, immunotherapy therapy with monoclonal antibodies, treatment with tyrosine kinase inhibitors, or radiotherapy (except for treatment of brain and

extremities) within the past four weeks prior to treatment with the trial drug, i.e., the minimum time elapsed since the last anticancer therapy and the first administration of BIBF 1120 must be four weeks
* Radiotherapy (except extremities and brain) within the past three months prior to baseline imaging
* Concomitant yellow fever vaccination
* Patients taking NSAIDS with short half lives unable or unwilling to interrupt NSAIDs for a five day period (2 days before pemetrexed, day of pemetrexed, 2 days after pemetrexed)
* Patients taking NSAIDS with long half lives must interrupt NSAID for 8 days (5 days before, day of and 2 days after treatment with pemetrexed)
* Active brain metastases (e.g. stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, requiring treatment with anti-convulsants; dexamethasone therapy will be allowed if administered as stable dose for at least one month before randomisation)
* Leptomeningeal disease
* Radiographic evidence of cavitary or necrotic tumors
* Centrally located tumors with radiographic evidence (ct or mri) of local invasion of major blood vessels
* History of clinically significant haemoptysis within the past 3 months (more than one teaspoon of fresh blood per day)
* Therapeutic anticoagulation (except low dose heparin and/or heparin flush as needed for maintenance of an indwelling intravenous device) or antiplatelet therapy (except for chronic low-dose therapy with acetylsalicylic acid *325mg per day)
* History of major thrombotic or clinically relevant major bleeding event in the past 6 months
* Known inherited predisposition to bleeding or thrombosis
* Significant cardiovascular diseases (i.e., hypertension not controlled by medical therapy, unstable angina, history of myocardial infarction within the past 6 months, congestive heart failure > NYHA II, serious cardiac arrhythmia, pericardial effusion)
* Calculated creatinine clearance by Cockcroft Gault <45ml/min
* Proteinuria ctcae grade 2 or greater
* Total bilirubin above the upper limit of normal
* ALT and/or AST > 2.5 x upper limit of normal in the presence of live metastasis or ALT and/or AST >1.5 x upper limit of normal in patients without liver metastasis.
* Prothrombin time and/or partial thromboplastin time greater than 50% deviation from normal limits
* Absolute neutrophil count (ANC) <1500 neutrophils /mm3
* Platelets <100,000 platelets/mm
* Haemoglobin <9.0 g/dL
* Significant weight loss (> 10 %) within the past 6 weeks prior to treatment in the present trial
* Current peripheral neuropathy * ctcae Grade 2 except due to trauma
* Pre-existing ascites and/or clinically significant pleural effusion
* Major injuries and/or surgery within the past ten days prior to randomisation with incomplete wound healing
* Serious infections requiring systemic antibiotic (e.g. antiviral, antimicrobial,

antifungal) therapy
* Decompensated diabetes mellitus or other contraindication to high dose corticosteroid therapy
* Gastrointestinal disorders or abnormalities that would interfere with absorption of the study drug
* Active or chronic hepatitis C and/or B infection
* Serious illness or concomitant non-oncological disease such as neurologic-, psychiatric-, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the patient inappropriate for entry into the study
* Patients who are sexually active and unwilling to use a medically acceptable method of contraception (e.g. such as implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner for participating females, condoms for participating males) during the trial and for at least twelve months after end of active therapy
* Pregnancy or breast feeding
* Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule
* Patients unable to comply with the protocol
* Active alcohol or drug abuse
* Other malignancy within the past three years other than basal cell skin cancer, or carcinoma in situ of the cervix
* Any contraindications for therapy with pemetrexed
* History of severe hypersensitivity reactions to pemetrexed or other drugs formulated with mannitol
* Hypersensitivity to BIBF 1120 and/or the excipients of the trial drugs
* Hypersensitivity to contrast media

Study design

Design

Study phase:	3
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):	30-09-2009
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BIBF 1120
Generic name:	NAP
Product type:	Medicine
Brand name:	Pemetrexed
Generic name:	Alimta
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-11-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-05-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2009

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-10-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-12-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-01-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-08-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	01-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-05-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-11-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2008-002072-10-NL
CCMO	NL24486.078.08