A Randomized Discontinuation Study of Brivanib alaninate (BMS-582664) versus Placebo in Subjects with Advanced Tumors.

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Compare Progression Free Survival (PFS) for brivanib versus placebo in subjects with advanced solid tumors with FGF-2 over-expression and who have obtained stable disease after 12 weeks of treatment with brivanib separately for each tumor.

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

Summary

ID

NL-OMON32125

Source
ToetsingOnline

Brief title
CA182-026

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Advanced Tumors

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: BMS-582664, Cancer, Phase 2

Outcome measures

Primary outcome

The primary outcome measure is Progression*free Survival (PFS) time defined as

the length of time during

and after treatment in which a patient is living with a disease that does not

get worse. In this trial the PFS of

patients with advanced solid tumours who have achieved disease stabilization

after an initial 12*week

treatment with brivanib and are randomized to continue treatment will be

compared to those who are

randomized to receive a placebo. Subjects who did not progress nor die will be

censored at the date of the last tumour measurement.

Secondary outcome

The secondary outcome measures include:

•Objective response rate defined as the percentage of patients whose cancer

shrinks or disappears during

and after treatment based on an established method of imaging and measurement

of tumour lesions.

•Duration of response defined as the length of time between the detection of

tumour size reduction or

disappearance and the recurrence or worsening of the disease.

•Time to response defined as the length of time from the start of study

treatment and the detection of tumour

size reduction or disappearance

•Disease stabilization rate defined as the percentage of patients whose cancer

does not grow or shrink during

study treatment

•Safety of study treatment defined by the number and seriousness of adverse

events associated with brivanib

•Evaluation of biomarkers (such as Collagen IV, soluble VEGF and VEGF*receptor,

or soluble FGF) isolated

from patient blood samples and correlated with the clinical course of disease

and response to study

treatment

Study description

Background summary

Brivanib is a small molecule tyrosine kinase potent inhibitor of the vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) family of receptors. Its clinical development is focused in three main areas; VEGF driven tumors, VEGF resistant tumors with targeting of FGF signaling pathways, and FGF driven tumor biology. This trial is the proof of principle trial to demonstrate that brivanib has activity when given as a single agent to subjects with advanced solid tumors where the tumor over-expresses FGF-2 ligand protein as demonstrated by immunohistochemistry.

Study objective

Compare Progression Free Survival (PFS) for brivanib versus placebo in subjects with advanced solid tumors with FGF-2 over-expression and who have obtained stable disease after 12 weeks of treatment with brivanib separately for each tumor.

Study design

The main purpose of the study is to determine the effects of brivanib versus placebo in patients with stable disease after 12 weeks of brivanib treatment. Those patients who during the 12 weeks have clearly showed benefit will continue treatment with brivanib and those who*s tumour has progressed will come off study. For those patients in which it is unclear if they are benefiting ie stable disease, half will continue on treatment and half will stop treatment and switch to placebo. If the patient becomes substantially worse on placebo they can restart brivanib treatment.

The study is divided into two parts. The initial phase is an open label lead-in which has been designed to determine which patients to include or exclude from the second randomised portion of the study which focuses on investigating which patients are likely to benefit from treatment.

All tumour types will be considered with initial focus on advanced non-small cell lung, transitional cell carcinoma, soft tissue sarcoma, gastric/oesophageal adenocarcinoma or pancreatic cancer including ampulla of Vater tumours. Should any tumour type have a low proportion of subjects randomised into the second phase then the Study Steering Committee may cease enrolment for that tumour type and another tumour type may be substituted, these include: refractory prostate cancer, ovarian cancer, breast cancer, endometrial cancer, melanoma, or head and neck cancer.

All qualifying patients will receive a daily dose of brivanib for up to 12 weeks. At the week 12 visit, if the tumour is assessed as stable according to the Modified WHO criteria the patient will enter the double blind part of the trial where they will be assigned to receive either brivanib or placebo at a 1:1 ratio stratified according to tumour type and FGF-2 status. For those patients who show a >=50% reduction in tumour size they will continue on brivanib treatment open-label. For those who show a >= 25% increase in tumour size they will stop treatment and discontinue from the study.

Intervention

All subjects will receive brivanib during the initial 12 week run in period. Subjects achieving stable disease at week 12 will be randomized to either brivanib or matching placebo. Brivanib (BMS-582664) or placebo will be self-administered orally on a continuous daily schedule of 800 mg until disease progression or unacceptable toxicity.

Study burden and risks

There is a possibility that BMS-582664 may be an effective treatment for some types of cancer. However, it is not known if individual patients entering the trial will benefit directly. The information gained from this study may help future patients with advanced cancer. Patients will have the inconvenience of more frequent interventions/procedures and longer visits to the hospital than would be usual for routine clinical care. They will also have to undergo additional procedures. Potential side effects are known from research studies in a small number of subjects. Additional unforeseen side effects could occur and some side effects could be life-threatening or fatal. Safety monitoring is included throughout the protocol. At all times throughout the study, the patient has the right to withdraw consent without their usual standard of care being affected.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

• Histologic or cytologic confirmed diagnosis of a solid tumor (non-small cell lung, gastric/esophageal adenocarcinoma, soft tissue sarcoma, transitional cell carcinoma and pancreatic cancer including ampulla of Vater tumors) which has progressed on standard therapy or for whom no standard therapy is known.
• Measurable disease
• Men and women, age 18 or older
• Life expectancy at least 3 months
• ECOG performance status 0 or 1 (generally fit and mobile)
• Adequate tumor sample for FGF-2 assay
• Adequate bone marrow, renal and hepatic function
• Adequate recovery from recent surgery and radiation therapy - one week for minor surgery and 8 weeks for major surgery or radiation therapy.
• At least 3 weeks must have relapsed since last dose of chemotherapy or targeted agents providing the subject has recovered from all toxicities. At least 8 weeks must have elapsed from the last dose of bevacizumab, prior to beginning protocol therapy.

Exclusion criteria

• Women of child bearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy during study and up to 12 weeks after the last dose of drug, are pregnant or breastfeeding or have a positive pregnancy test on enrollment or prior to investigational product administration.
• Sexually active fertile men not using effective birth control if their partners are WOCBP, including up to 12 weeks after the last dose of investigational product.
• Actual diagnosis of brain metastasis or any known signs and symptoms, unless confirmed negative by means of a CT scan.
• Centrally cavitating lung lesions.
• History of thrombo-embolic disease within the last six months requiring therapy.
• Other primary malignancy except carcinoma in situ of cervix or urinary bladder or non-melanoma skin cancer.
• History of poor wound healing or non healing ulcers
• Uncontrolled or significant cardiovascular disease including myocardial infarction within 12 months, uncontrolled angina within 12 months; congestive heart failure (Class III-IV New York Heart Association (NYHA) and valvular heart disease grade 2.
• Uncontrolled hypertension even despite appropriate treatment.
• History of stroke, transient ischemic attack or other ischemic event.
• Mental incapacitation or psychiatric illness which would preclude study participation.
• Inability to swallow tablets or untreated malabsorption syndrome.
• History of allergy to brivanib its drug class or related compounds.
• Exposure to any investigational drug within 4 weeks of enrollment
• Other concurrent chemotherapy, hormonal therapy, immunotherapy regimens or

radiotherapy, standard or investigational. Subjects may continue to receive hormone replacement therapy.
• Prior exposure to brivanib.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-01-2009
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	brivanib
Generic name:	tyrosine kinase inhibitor

Ethics review

Approved WMO

Date:	22-08-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	26-11-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-04-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2009
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-09-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-10-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-11-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-03-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-06-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-08-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2011
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:	28-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-08-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-06-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	28-06-2012
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	EUCTR2008-000087-16-NL
ClinicalTrials.gov	NCT00633789
CCMO	NL22044.078.08