A Double-Blind, Randomized Phase III Study Evaluating the Efficacy and Safety of Sorafenib Compared to Placebo in Locally Advanced/Metastatic RAI-Refractory Differentiated Thyroid Cancer

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Thyroid gland disorders
Study type	Interventional

Summary

ID

NL-OMON39366

Source
ToetsingOnline

Brief title
SORAFENIB- 14295

Condition

- Thyroid gland disorders

Synonym
cancer;

Research involving
Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: farmaceutisch bedrijf

Intervention

Keyword: cancer, differentiated, metastase, thyroid

Outcome measures

Primary outcome

Primary endpoint:

* Progression-Free Survival (PFS)

Secondary outcome

Secondary endpoints:

* Overall Survival (OS)

* Time to Progression (TTP)

* Disease Control Rate (DCR)

* Response Rate (RR)

* Duration of Response (DoR)

* Safety, which will include assessment of adverse events and abnormalities in

laboratory parameters

* Exposure of sorafenib (AUC(0-12)) by population pharmacokinetic methods

Study description

Background summary

Sorafenib is a tablet that is already approved by the Food and Drug Administration (FDA), EMEA and other Health Authorities around the world for the treatment of advanced kidney cancer and for liver cancer. Bayer Healthcare

AG manufactures the drug, sorafenib, also known as Nexavar®.. To date, over 39,000 cancer patients have taken sorafenib either by itself or together with other common chemotherapy drugs. Sorafenib works by slowing down, and/or stopping the development of new cancer cells and new blood vessels. By stopping the growth of new blood vessels around a tumor, it is believed that sorafenib prevents the growth of tumors.

Study objective

The purpose of this study is to find out if patients with locally advanced/metastatic Radioactive Iodine-refractory (RAI) thyroid cancer (papillary, follicular or Hurthle cell carcinoma), will benefit from sorafenib treatment compared to patients who receive placebo (sugar pills). The goal of the study is to test the ability of sorafenib to prolong the Progression-Free Survival (PFS). This means we would like to see if sorafenib stops your tumor from growing. If you were receiving placebo, you may have the option to cross-over to sorafenib if your study doctor feels your tumor(s) may be increasing in size or a new tumor may be evident.

Study design

This study is designed as a *randomized*, *placebo-controlled* and *double-blind* study.
This study is divided into 4 different periods:

Screening Period
Double Blind Treatment Period
Open Label Treatment Period
Long Term Follow up Period

Intervention

Double blind:
Each morning, at approximately the same time, the patient takes two tablets of the study medication (sorafenib (200 mg) or placebo) from the supply provided by the doctor. In the evening, at approximately the same time, he/she takes two more tablets.

Open-label:
After unblinding, in case you have received placebo the patient will be given the opportunity to *cross-over* from receiving placebo and begin to receive sorafenib in the open-label treatment period. If the patient has received sorafenib and the study doctor believes that he/she still is benefiting from the sorafenib treatment he/she will be allowed to continue sorafenib.

Study burden and risks

Very Common side-effects: = 10% or more
Effects on the skin (rash, itching, and redness of the skin and, redness and peeling of the hands and feet that may cause blistering and pain) and hair loss; digestive symptoms (feeling like or actually throwing up, diarrhea); high blood pressure (hypertension); bleeding from the mouth, nose, areas in the body where food pass, including the stomach [gastrointestinal tract], the end of the intestines [rectum], airways [respiratory tract], the brain (the bleeding in the gastrointestinal tract, the respiratory tract and in the brain may have a life-threatening or fatal outcome); feeling tired, pain (including pain in the head, mouth and abdomen and pain associated with the tumor or tumor in the bone) and abnormal changes to blood tests (including reduction of white blood cells leading to an increased risk of infection, low phosphate levels and increased blood levels of enzymes from the pancreas).

The patient will be monitored carefully.

Contacts

Public
Bayer

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US
Scientific
Bayer

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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

* Locally advanced or metastatic differentiated thyroid cancer (papillary, follicular and Hurthle cell)
* Progression within 14 months (RECIST should be used as a basis for the assessment of disease progression)
* RAI refractory: patients will be deemed to be refractory to radioactive iodine (RAI) if they have a known tumor lesion that qualifies as a target lesion per the protocol RECIST criteria, and that target lesion has no iodine uptake on a post-radioactive-iodine scan performed under conditions of a low iodine diet and adequate TSH elevation or rhTSH stimulation.;Certain patients whose tumors have iodine uptake may also be eligible for participation. They include the following categories of patients:;o Patients who have some iodine uptake, who have had a radioactive iodine treatment (>100mCi)within the last 16 months, and who have had progression (by RECIST) of their target lesion(s) despite that RAI treatment (which was performed under conditions of a low iodine diet and adequate TSH elevation or rhTSH simulation);;OR
o Patient who have some iodine uptake, who have had multiple RAI treatments, whose last RAI treatment was >16 months ago, and who had progression after each of two RAI treatments (>100mCi each) that were done within 16 months of each other (and which were each performed under conditions of a low iodine diet and adequate TSH elevation of rhTSH simulation;;OR
o Any individual patient who has received RAI treatments with a cumulative RAI dose of >600mCi.
* Not a candidate for surgery or radiotherapy with curative intent.
* Subjects with at least one measurable lesion. Lesions must be measured by CT-scan or MRI (Magnetic Resonance Imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST Criteria (v1.0). For this study, bone lesions are considered to be measurable and eligible as target lesions if they are lytic lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI and the soft tissue component meets the definition of measurability according to RECIST (vs. 1.0).
* Availability of histological material for central review of the diagnosis of differentiated thyroid cancer
* Adequate TSH-suppression (< 0.5 mU/l)
* Age > 18 years
* Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 14 days prior to randomization:
* Hemoglobin > 9.0 g/dl
* Absolute neutrophil count (ANC) >1,500/mm3
* Platelet count * 100,000/mm3
* Total bilirubin < 1.5 times the upper limit of normal
* Alanine transaminase (ALT) and Aspartate aminotransferase (AST) < 2.5 x upper limit of normal
* Prothrombin time (PT)/international normalized ratio (INR) and partial thromboplastin time

(PTT) < 1.5 x ULN
* Serum creatinine < 1.5 x ULN.
* Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
* Life expectancy of at least 12 weeks.
* Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of treatment. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
* Women and men of childbearing potential must agree to use adequate contraception (barrier method of birth control) since signing of the informed consent form until at least 30 days after the last study drug administration.
* Subjects must be able to understand and willing to sign a written informed consent. A signed informed consent must be appropriately obtained prior to any study specific procedures.
* Subjects must be able to swallow and retain oral medication.

Exclusion criteria

* Histologic subtypes of thyroid cancer other than differentiated (i.e. like anaplastic and medullary carcinoma, lymphoma or sarcoma).
* Prior anticancer treatment with tyrosine kinase inhibitors, monoclonal antibodies (licensed or investigational) that target VEGF or VEGF Receptors or other targeted agents.
* Prior anti-cancer treatment for thyroid cancer with use of chemotherapy (low dose chemotherapy for radiosensitization is allowed) or Thalidomide or any of its derivatives.
* Major surgery, open biopsy, or significant traumatic injury within 30 days prior to randomization.
* Non-healing wound, ulcer, or bone fracture.
* Evidence or history of bleeding diathesis or coagulopathy disorder.
* Subjects with tracheal, bronchial or esophageal infiltration with significant risk of bleeding without having received local treatment prior to enrollment in the study.
* Clinically significant cardiac disease including congestive heart failure > class II New York Heart Association (NYHA), unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months) or myocardial infarction within the past 6 months prior to randomization.
* Cardiac ventricular arrhythmias requiring anti-arrhythmic therapy or uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg) despite optimal medical management.
* Thrombotic or embolic venous or arterial events, such as a cerebrovascular accident, including transient ischemic attacks, arterial thrombosis, deep vein thrombosis and pulmonary embolism within the past 6 months.
* Hemorrhage/bleeding event * NCI-Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 within 3 months of randomization.
* Infection > NCI-CTCAE Grade 2.
* Known human immunodeficiency virus infection or infection with hepatitis B or C.
* Previous or concurrent cancer that is distinct in primary site or histology from thyroid

cancer within 5 years prior to randomization EXCEPT cervical cancer in situ, treated basal cell carcinoma and superficial bladder tumors [Ta (Non invasive tumor), Tis (Carcinoma in situ) and T1 (Tumor invades lamina propria)].
* Known or suspected allergy to sorafenib or hypersensitivity to sorafenib or any agent given in the course of this trial.
* Subjects with seizure disorder requiring medication (such as steroids or anti-epileptics).
* Subjects undergoing renal dialysis.
* Substance abuse, medical, psychological or social conditions that may interfere with the patient*s participation in the study or evaluation of the study results.
* Unresolved toxicity (i.e. neurotoxicity) attributed to any prior therapy higher than NCI-CTCAE (version 3) Grade 2 (excluding cases of alopecia).
* Any malabsorption condition.
* Any condition that is unstable or could jeopardize the safety of the patient and their compliance in the study.
* History of brain metastases allowed, provided definitive therapy (surgery and/or radiation) has been administered before randomization, no further treatment of brain metastases is planned; the subject is clinically stable for at least 2 weeks before study treatment (Prior and ongoing corticosteroid treatment is allowed, provided the dose is not high, stable and no dose adjustments are needed after randomization).
* Pregnant or breast-feeding subjects. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. All subjects of child-bearing potential must use adequate birth control measures during the course of the trial (barrier method of birth control).

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):	07-07-2010

Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nexavar
Generic name:	Sorafenib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	20-10-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-02-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-10-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-05-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-12-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO Date:	26-01-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-06-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-06-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-07-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-10-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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
Other	1
EudraCT	EUCTR2009-012007-25-NL
CCMO	NL29757.058.09

Study results

Date completed:	26-10-2016
Actual enrolment:	8