An Open-label, Randomized Phase 3 Study of the Efficacy and Tolerability of Linifanib (ABT-869) versus Sorafenib in Subjects with Advanced Hepatocellular Carcinoma (HCC)

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

Summary

ID

NL-OMON34685

Source
ToetsingOnline

Brief title
M10-963

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary neoplasms malignant and unspecified

Synonym
hepatoma, Liver cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Abbott
Source(s) of monetary or material Support: Industrie (Abbott B.V.)

Intervention

Keyword: Hepatocellular Carcinoma, Linifanib, Phase 3, Sorafenib

Outcome measures

Primary outcome

The primary efficacy analysis will be a comparison of overall survival (OS) distributions between the linifanib and sorafenib treatment groups.

Time to death for a given subject will be defined as the number of days from the date that the subject was randomized to the date of the subject's death.

All events of death (up to the 667th death for final analysis) will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has not died, then the data will be censored at the date when the subject was last known to be alive.

Secondary outcome

Secondary efficacy analyses comparing the effects of linifanib versus sorafenib will also be performed on time to progression (TTP) and objective response rate (ORR). Time to progression will be defined as the number of days from the date of randomization to the date of earliest disease progression, per RECIST (version 1.1). All disease progression will be included regardless of whether the event occurred while the

subject was taking the study drug or had previously discontinued the study

drug. If the subject does not experience disease progression, then the data will be censored at the date of last radiographic tumor assessment. If the subject does not experience disease progression and does not have any radiographic tumor assessment, then the subject will be censored at the date of randomization. Objective response rate is defined as the proportion of subjects with complete or partial response per RECIST (version 1.1); all response assessments must be confirmed by scans not less than 4 weeks apart.

Study description

Background summary

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most common cause of mortality. There are approximately 560 000 new cases diagnosed each year. Additionally, over half a million deaths can be attributed to liver cancer annually.

Although there is a wide geographic variety in HCC incidence, the majority of the HCC cases (>80%) occur in sub-Saharan Africa and in eastern Asia. In these regions, infection with the Hepatitis B virus (HBV) and dietary exposure to aflatoxin B1 are the primary risk factors. In other areas of the world, such as the United States and Europe, the Hepatitis C virus (HCV) and alcohol consumption are the principal risk factors. It is these regions where HCC incidence is on the rise. Across all geographic regions the incidence of HCC among men is two to four times higher than that is seen in females. The most common and unifying condition associated with HCC is cirrhosis, which develops after long latencies of chronic liver disease.

Patients will have compromised liver function as a result of both cirrhosis and/or tumor replacement. Many subjects with HCC also have portal hypertension contributing to hepatic dysfunction. Despite the fact that primary curative treatment is resection, subjects are often inoperable because of marginal liver function or unresectable due to portal vein involvement or distant metastases. For the 80% of patients with unresectable tumors, the median survival is 4 months.

HCC is known to be a highly vascular tumor and overexpresses vascular endothelial growth factor (VEGF). One multiple tyrosine kinase

inhibitor/anti-angiogenic agent (sorafenib) has been approved for the treatment of unresectable HCC and other anti-angiogenic agents are under phase 3 clinical investigation.

Study objective

The primary objective of this study is to assess the overall survival (OS) of oral linifanib given as monotherapy daily (QD) compared to sorafenib given twice daily (BID) per standard of care in subjects with advanced or metastatic HCC. The secondary objectives of this study are to assess time to progression (TTP) and objective response rate (ORR) in those subjects treated with linifanib compared with sorafenib. The tertiary objectives are to assess progression free survival (PFS) and quality of life (QoL).

Study design

This is a Phase 3, randomised, open-label, multinational, multicenter study to evaluate the efficacy and tolerability of linifanib compared to to sorafenib in subjects with advanced or metastatic HCC who have not received prior systemic therapy.

Subjects will be randomized in a 1:1 ratio to 1 of the 2 treatment groups (linifanib or sorafenib). Approximately 900 subjects will be enrolled at approximately 200 sites. Two interim analyses are planned.

Intervention

During the study, patients will receive oral linifanib (17.5 mg once a day) or oral sorafenib (400 mg twice a day).

Patients that are in the linifanib treatment arm will have to take their medication under fasting conditions. Fasting is described as no food and beverages for 2 hours before and after treatment dosing.

Study burden and risks

The use of linifanib or sorafenib will cause side effects, which will be discussed with the patient, and is displayed in the patient information.

Risks of blood samples being drawn include pain, bruising, bleeding, inflammation, infection, temporary redness of the skin at the injection site and light-headedness.

The MUGA scan will be done using a radioactive tracer. The amount of radiation is very low and does not cause radiation sickness. In rare occasions, this can cause allergic reactions.

Subjects receiving anti-angiogenic therapy like linifanib may be at a higher risk of bleeding and blood clots. Other drugs in this class have had complications of wound healing.

As the endpoints of this study are not displayed in time, it is not possible to predict the amount of times the patient has to return to the hospital for a visit.

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

Each subject must fulfill all of the following criteria within 21 days prior to the first day of therapy.
1) Subject must be >= 18 years of age.

2) Subject must be diagnosed with unresectable or metastatic HCC defined by:
* Histologic or cytologic diagnosis OR
* European Association for the Study of Liver Criteria
3) Radiological criteria: two coincident imaging techniques (Four techniques considered: ultrasound, spiral computed tomography (CT), magnetic resonance imaging (MRI) and angiography)
4) Focal lesion > 2 cm with arterial hypervascularization
5) Combined criteria: one imaging technique associated with AFP (alpha fetoprotein) > 400 ng/mL
6) Subjects must have a measurable lesion by RECIST version 1.1 on CT scan in at least one site
which has not received prior radiotherapy.
7) Subjects must show signs of progression (i.e., new lesion per RECIST version 1.1) if prior liver-directed therapy was received.
8) Subject has an Eastern Cooperative Oncology Group (ECOG) Performance status of 0 to 1.
9) Subject must have the following laboratory values:
* Total Bilirubin <= 3.0 mg/dL or equivalent
* AST/ALT <= 5 × ULN
* PTT <= 1.5 × ULN and INR < 1.5
* ANC >= 1.0 × 109/L
* Platelet count >= 50 × 109/L if splenomegaly; if splenomegaly is not present, platelet count >= 75 × 109/L
* Creatinine <= 1.5 × ULN
* Serum albumin >= 2.8 g/dL
* PT <= 6 seconds prolonged
10) Women of childbearing potential and men must agree to use adequate contraception prior to
study entry, for the duration of study participation and for 90 days following completion of therapy. Women of childbearing potential must have a negative urine pregnancy test within 7 days prior to initiation of treatment and/or post-menopausal women must be amenorrheic for
at least 12 months to be considered of non-childbearing potential.
11) Subject is capable of understanding and complying with parameters as outlined in the protocol and able to sign informed consent, approved by an Independent Ethic Committee (IEC)/Institutional Review Board (IRB) prior to the initiation of any screening or study-specific procedures, and in the opinion of the Study Investigator with agreement by the subject, currently no other treatment options exist that will provide benefit to the subject and/or the subject is willing to receive (e.g., transcatheter arterial chemoembolization).

Exclusion criteria

1) Subject has received prior systemic (administered intravenously or orally rather than locoregionally) treatment for HCC.
2) Subject has Child-Pugh grade Class B or C hepatic impairment.
3) Subject has received prior local therapy (including liver-directed therapy) within 4 weeks

prior
to study drug administration. Local therapies include but are not limited to: surgery, radiation therapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection or cryoablation. In addition, subject has not recovered to <= Grade 1 clinically significant adverse effects/toxicities of previous therapy.
4) Subject has untreated brain or meningeal metastases. CT scans are not required to rule out
brain or meningeal metastases unless there is a clinical suspicion of central nervous system disease. Subjects with treated brain metastases that are radiographically or clinically stable (for
at least 4 weeks after therapy) and have no evidence of cavitation or hemorrhage in the brain
lesion, are eligible provided that they are asymptomatic and do not require corticosteroids (must
have discontinued steroids at least 1 week prior to Study Day 1).
5) Subject has previous or concurrent cancer that is distinct in primary site or histology from HCC
except cervical carcinoma in situ, non-melanoma carcinoma of the skin or in situ carcinoma of
the bladder. Any cancer curatively treated greater than 3 years prior to entry is permitted.
6) The subject has proteinuria defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade > 1 at baseline as measured by a urine dipstick (2+ or greater) and confirmed by a 24 hour urine collection (> 1 g/24 hrs). Subjects may be re-screened if proteinuria is shown to be controlled with or without intervention.
7) Subject currently exhibits symptomatic or persistent, uncontrolled hypertension defined as diastolic blood pressure > 90 mmHg or systolic blood pressure > 140 mmHg. Subjects may be
re-screened if blood pressure is shown to be controlled with or without intervention.
8) The subject has a documented Left Ventricular Ejection Fraction < 50%.
9) Subject is receiving therapeutic anticoagulation therapy. Low dose anti coagulation (e.g., low
dose warfarin) for catheter prophylaxis only will be permitted. No low molecular weight heparin (LMW) is allowed.
10) Subject is receiving anti-retroviral therapy for Human Immunodeficiency Virus (HIV). Prophylactic antiviral therapy to prevent Hepatitis B virus (HBV) reactivation is allowed.
11) Female subjects who are pregnant or breast feeding.
12) Presence of > grade 2 encephalopathy by NCI CTCAE criteria.
13) Presence of >= grade 2 ascites by NCI CTCAE criteria.
14) Clinically significant uncontrolled condition(s).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-05-2010
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Does not have a specialité name yet
Generic name:	Linifanib
Product type:	Medicine
Brand name:	Nexavar
Generic name:	Sorafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-12-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-03-2010
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-05-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2009-013435-38-NL
ClinicalTrials.gov	NCT01009593
CCMO	NL30198.029.09