A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF TIVANTINIB (ARQ 197) IN SUBJECTS WITH MET DIAGNOSTIC-HIGH INOPERABLE HEPATOCELLULAR CARCINOMA (HCC) TREATED WITH ONE PRIOR SYSTEMIC THERAPY

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The most important purpose of this scientific study is to determine whether the use of tivantinib is safe and effective in patients with liver cancer in which the MET-protein is present in high concentration.

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

Summary

ID

NL-OMON41234

Source
ToetsingOnline

Brief title
Evaluation of tivantinib on safety and effectivenes with liver cancer

Condition

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

Synonym
Hepatocellular Carcinoma, Liver cancer

Research involving
Human

Sponsors and support

Primary sponsor: Daiichi Pharmaceutical
Source(s) of monetary or material Support: Daiichi Sankyo;UK

Intervention

Keyword: Hepatocellular carcinoma, Liver cancer, MET-high

Outcome measures

Primary outcome

Evaluate overall survival (OS) among all subjects in the intent-to-treat (ITT)

population compared to

placebo.

Secondary outcome

Secondary:

* Evaluate progression free survival (PFS) by central, independent radiology

review among all subjects in

the intent-to-treat (ITT) population compared to placebo.

* Evaluate safety of tivantinib in the treated HCC subjects.

Exploratory:

* Evaluate objective response rate (ORR), disease control rate (DCR), time to

progression (TTP), and

type of progression, by central, independent radiology review among all

subjects in the intent-totreat (ITT) population compared to placebo.

* Evaluate pharmacokinetics of tivantinib and its metabolites in HCC subjects

and explore the factors, including CYP2C19 genotype, and major

strong CYP3A4/CYP2C19 inhibitors which may affect tivantinib pharmacokinetics

(PK) in HCC subjects.

* Explore the exposure-response relationship of tivantinib to biomarkers and to

safety and efficacy endpoints.

* Evaluate Functional Assessment of Cancer Therapy-Hepatobiliary

(FACT-Hep)-based FHSI-3 Pain Score (pain, pain in back, pain/discomfort in

stomach); FACT-Hepatobiliary Symptom Index (FHSI-8) score, Emotional Well Being

(EWB) score, and the FACT-Hep total score.

* Evaluate time-to-hospitalization (all-cause) and time-to-hospitalization

(HCC-related).

Study description

Background summary

Tivantinib is a MET inhibitor. MET is a protein that is found on several types of cells, including normal liver cells and liver cancer cells. The high levels of MET in liver cancer tumors are associated with tumor growth and progression. A drug that inhibits the activity of MET may be useful to treat liver cancer. In a recent clinical trial, MET-High patients were the ones who benefited the most by taking tivantinib.

Study objective

The most important purpose of this scientific study is to determine whether the use of tivantinib is safe and effective in patients with liver cancer in which the MET-protein is present in high concentration.

Study design

Global, multi-center, randomized, placebo-controlled, double-blind Phase 3 study designed to compare treatment of tivantinib versus placebo in subjects with MET Diagnostic-High (MET-High) (>= 50% of tumor cells with a staining intensity of >= 2+ for MET as assessed by immunohistochemistry in a central lab) inoperable HCC (where surgery is not indicated due to disease extension,

co-morbidities, or other technical reasons). Subjects must have had radiographic disease progression after one sorafenib containing systemic first line therapy or were
unable to tolerate sorafenib. Subjects are randomized to receive either tivantinib or placebo in a 2:1 ratio and are stratified based on vascular invasion (present or not), extra-hepatic spread including distant metastasis and/or involved regional or distant lymph nodes (present or not), and Alpha fetoprotein (AFP) (less/equal or greater than 200 ng/mL).

Intervention

Subjects are to continue therapy with study drug until death or radiographic progressive disease (PD) associated with clinical deterioration, or until another of the specified criteria is met for stopping therapy.

Study burden and risks

Average estimated duration of subject participation (screening/enrollment through follow-up): 1-7 months. Average estimated duration of subject treatment (from first to last dose of study drug): 1-5 months (some subjects may stay on treatment even less or more).

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

1. Written informed consent granted prior to initiation of any study-specific screening procedures;2. 18 years of age or older;3. Histologically confirmed HCC that is inoperable (where surgery is not indicated due to disease extension, co-morbidities, or other technical reasons) and not eligible for local therapy ;4. MET Diagnostic-High tissue reported by the central authorized laboratory using archival or recent biopsy tumor samples (see lab manual and Section 6.1 of protocol for tissue preparation details). ;5. Received at least 4 weeks of one prior sorafenib containing systemic therapy and then experienced documented radiographic disease progression; or inability to tolerate prior therapy received for at least a minimum period of time. For the purpose of this study, intolerance to sorafenib is determined as follows:;• The subject must have tried to take sorafenib for a period of at least 28 days (even intermittently) ;• The subject must have tried to dose reduce sorafenib at <=50% of the full dose for a period of at least 14 days (even intermittently) and still have a documented Grade >=2 toxicity;• A period of even less than 14 days on sorafenib is acceptable in case of:;i. Uncontrolled Grade 3 - 4 arterial hypertension;ii. Pancreatitis, cardiac event, encephalopathy related to sorafenib;iii. >= Grade 2 Hand-foot syndrome triggered even at 50% of the sorafenib dose;6. Discontinued prior systemic treatment or any investigational drug for at least 2 weeks (14 days) or for at least 3 weeks for IV anti-cancer drugs, prior to the study randomization ;7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) <= 1 (Appendix 17.2);8. Local or loco-regional therapy (i.e., surgery, radiation therapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) must have been completed >= 4 weeks prior to randomization and are allowed. ;9. Measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Tumor lesions previously treated with local therapy should demonstrate clear dimensional increase by radiographic assessment in order to be selected as target lesion(s) at baseline. Baseline radiographic assessment needs to be done within 21 days prior to randomization. ;10. Adequate bone marrow, liver, and renal functions at Screening Visit, defined as: platelet count >= 60 × 109/L; hemoglobin >= 9.0 g/dL; absolute neutrophil count (ANC) >= 1.5 × 109/L; total bilirubin <= 2 mg/dL; Alanine transaminase (ALT) and aspartate aminotransferase (AST) <= 5 × upper limit of normal (ULN); serum creatinine <= 1.5 × ULN; albumin >= 2.8 g/dL; international normalized ratio (INR) 0.8 to ULN or <= 3 for subjects receiving anticoagulant such as coumadin or heparin. Subjects who are therapeutically anticoagulated are allowed to participate provided that prior to anticoagulant therapy no evidence of underlying defect in coagulation exists ;11. Women of childbearing potential must have a negative serum pregnancy test performed within 14 days prior to the randomization (where demanded by local regulations, test may be required within 72 hours prior to randomization);12. Male and female subjects of child-bearing potential must agree to use double-barrier contraceptive

measures, oral contraception, or avoidance of intercourse during the study and for 90 days after last study drug dose received;13. Life expectancy of at least 12 weeks

Exclusion criteria

1. >1 prior systemic regimen (prior MET inhibitors/antibodies are not allowed; experimental systemic therapy for inoperable HCC given before or after sorafenib counts as separate regimen and is not allowed);2. Child-Pugh B-C cirrhotic status based on clinical findings and laboratory results during screening period (see Appendix 17.4 for Child-Pugh Classification and interpretation of ascites at physical examination and Prothrombin Time (PT)/ International Normalized Ratio (INR));3. Previous or concurrent cancer that is distinct from HCC in primary site or histology, EXCEPT cervical carcinoma in situ, treated basal cell carcinoma, and superficial bladder tumors (Ta, Tis & T1). Any cancer curatively treated > 3 years prior to enrollment is permitted.;4. History of congestive heart failure defined as Class II to IV per New York Heart Association (NYHA) classification (see Appendix 17.5) within 6 months prior to study entry; active coronary artery disease (CAD); clinically significant bradycardia or other uncontrolled, cardiac arrhythmia defined as >= Grade 3 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, or uncontrolled hypertension; myocardial infarction occurring within 6 months prior to study entry (myocardial infarction occurring > 6 months prior to study entry is permitted);5. Active clinically serious infections defined as >= Grade 3 according to NCI CTCAE, version 4.03;6. Any medical, psychological, or social conditions, particularly if unstable, including substance abuse, that may, in the opinion of the Investigator, interfere with the subject*s safety or participation in the study, protocol compliance, or evaluation of the study results;7. Known human immunodeficiency virus (HIV) infection;8. Blood or albumin transfusion within 5 days prior to the blood draw being used to confirm eligibility;9. Concomitant interferon therapy or therapies for active Hepatitis C Virus (HCV) infection;10. Pregnancy or breast-feeding;11. History of liver transplant;12. Inability to swallow oral medications;13. Clinically significant gastrointestinal bleeding occurring <= 4 weeks prior to randomization

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):	14-11-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tivantinib
Generic name:	Tivantinib

Ethics review

Approved WMO Date:	30-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-10-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2016
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	EUCTR2012-003308-10-NL
ClinicalTrials.gov	NCT01755767
CCMO	NL43348.018.13