A Multicenter, Randomized, Double-Blind, Phase 3 Study of Ramucirumab (IMC-1121B) Drug Product and Best Supportive Care (BSC) Versus Placebo and BSC as Second-Line Treatment in Patients With Hepatocellular Carcinoma Following First-Line Therapy With Sorafenib

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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-OMON37858

Source
ToetsingOnline

Brief title
REACH

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
Hepatocellular carcinoma, primary livercancer

Research involving
Human

Sponsors and support

Primary sponsor: ImClone LLC
Source(s) of monetary or material Support: ImClone

Intervention

Keyword: Hepatocellular carcinoma, Overall survival, Ramucirumab

Outcome measures

Primary outcome

- overall survival

Secondary outcome

The secondary efficacy endpoints to be analyzed are:

* Progression-free survival

* Best objective response rate

* Time to radiographic progression

* Patient-reported outcomes

Study description

Background summary

Inhibition of angiogenesis is considered a promising approach to the treatment of cancer. Members of the VEGF family and the VEGFR-2 are important mediators of angiogenesis and are likely important therapeutic targets in advanced HCC. Angiogenesis appears integral
to HCC development and pathogenesis. Angiogenesis inhibition has been efficacious in both in vitro and in vivo HCC models and results of clinical studies also suggest potential to inhibit disease growth.

Disabling the function of the VEGFR-2 or VEGFR-1 signaling pathway via a number of approaches has been shown to inhibit new blood vessel formation and tumor growth in a variety of animal models. Therapeutic agents that interfere with the function of VEGF and its receptors may represent efficacious approaches to antiangiogenic and antitumor therapy.
Ramucirumab is a recombinant human MAb that specifically binds to the extracellular domain of VEGFR-2 with high affinity. Phase 1 and 2 studies have demonstrated safety and tolerability at clinically relevant doses, with preliminary evidence of clinical efficacy in a variety of human cancers, including unresectable HCC and renal cancer refractory to sorafenib and/or sunitinib.

Study objective

The primary objective is to compare the overall survival (OS; time from randomization to death) in patients with hepatocellular carcinoma (HCC) who had disease progression during or following sorafenib therapy, or were intolerant to this agent. Patients will receive either ramucirumab (IMC-1121B) drug product (hereafter referred to as ramucirumab DP) plus best supportive care (BSC) or placebo plus BSC.

Secondary objectives are to evaluate:
* Progression-free survival (PFS)
* Best objective response rate (ORR)
* Time to radiographic progression
* Patient-reported outcome (PRO) measures of disease-specific symptoms and health-related quality of life
* Safety profile of ramucirumab DP
* Ramucirumab serum concentrations
* Pharmacodynamics of ramucirumab
* Immunogenicity of ramucirumab

Study design

This is a Phase 3 multicenter, randomized study evaluating the safety and efficacy of ramucirumab DP plus BSC as a double-blind, placebo-controlled (placebo plus BSC) comparison.

Intervention

Group A: 2 weekly intravenous administration of Ramucirumab dosis of 8 mg/kg, combined with BSC.
Group B: 2 weekly intravenous administration of Placebo (histidine buffer) combined with BSC

Randomization group A: group B is 1:1

Study burden and risks

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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

* ECOG PS of 0 or 1
* Child-Pugh score of 9 (Child-Pugh A or B [B7 or B8])
* BCLC stage C or BCLC stage B not amenable to locoregional therapy or refractory to locoregional therapy

* diagnosis of HCC (excluding fibrolamellar carcinoma) in the absence of histologic or cytologic confirmation
* There are either clinical, laboratory, or radiographic findings consistent with a diagnosis of liver cirrhosis
* The patient has a liver mass measuring at least 2 cm with characteristic vascularization seen on either triphasic computed tomography (CT) scan or magnetic resonance imaging (MRI) with gadolinium.
* The patient has a serum alpha-fetoprotein (AFP) concentration greater than the institutional upper limit of normal (ULN).
* At least 1 measurable or evaluable lesion that is viable (ie, is vascularized), and has not been previously treated with
locoregional therapy. A lesion that has been previously treated will qualify as a measurable or evaluable lesion if there was demonstrable
progression following locoregional therapy.
* Previously treated with sorafenib and has discontinued sorafenib treatment at least 14 days prior to randomization. Patients may have experienced
* Radiographically documented disease progression during sorafenib therapy or after discontinuation of sorafenib therapy, or
* Discontinuation of sorafenib due to an adverse drug reaction, despite dose reduction by 1 level and BSC
* The patient has received sorafenib as the only systemic therapeutic intervention for advanced HCC. Any hepatic locoregional therapy that has been;administered prior to sorafenib is allowed, but not following sorafenib. Radiation to metastatic sites (eg, bone) following sorafenib therapy is permitted.;* Except where otherwise noted in the eligibility criteria, the patient has a resolution to grade * 1 by the NCI-CTCAE v. 4.0 of all clinically significant toxic effects of prior locoregional therapy, surgery, chemoembolization or sorafenib. ;Adequate organ function defined as:;* Total bilirubin < 3.0 mg/dL (51.3 *mol/L), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) * 5 × ULN;;* Serum creatinine * 1.2 × ULN or calculated creatinine clearance > 50 mL/minute;;* Absolute neutrophil count (ANC) * 1.0 × 10exp3/*L (1.0 × 10exp9/L), hemoglobin * 9 g/dL (5.58 mmol/L), and platelets * 75 × 10exp3/*L (75 × 10exp9/L);;* International Normalized Ratio (INR) * 1.5. Patients receiving prophylactic low dose anticoagulant therapy are eligible provided that INR * 1.5.;* The patient's urinary protein is * 1+ on dipstick or routine urinalysis.;If urine dipstick or routine analysis indicates * 2+ proteinuria, then a 24-hour urine must be collected and must demonstrate < 1000 mg of protein in 24 hours to allow participation in the study.;* The study population is limited to patients with Child- Pugh Class A score without a history of hepatic encephalopathy or clinically meaningful ascites. Clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis

Exclusion criteria

* Major surgery within 28 days prior to randomization, or central venous access device placement within 7 days prior to randomization. ;* Hepatic locoregional therapy within 28 days prior to randomization. ;* Radiation to any nonhepatic (eg, bone) site within 14 days

prior to randomization. ;* Sorafenib within 14 days prior to randomization. ;* Received any investigational therapy or non-approved drug within 28 days prior to randomization or is concurrently enrolled in any other type of medical research judged not to;be scientifically or medically compatible with this study. ;* Received any previous systemic therapy with vascular endothelial growth factor (VEGF) inhibitors or vascular endothelial growth factor receptor (VEGFR) inhibitors (including investigational agents) other than sorafenib for treatment of HCC. ;* Fibrolamellar carcinoma. ;* Received any transfusion, blood component preparation, erythropoietin, albumin preparation, or granulocyte colony-stimulating factors (G-CSF) within 14 days prior to randomization. ;* Therapeutic anticoagulation with warfarin, low-molecular-weight heparin, or similar agents. Patients receiving prophylactic, low-dose anticoagulation therapy are eligible provided that the coagulation parameters defined in the inclusion criteria (INR * 1.5) are met. ;* Receiving ongoing therapy with nonsteroidal anti-inflammatory agents (NSAIDs, eg, indomethacin, ibuprofen, naproxen, nimesulide, celecoxib, etoricoxib, or similar agents) or other antiplatelet agents (eg, clopidogrel, ticlopidine, prasugrel, dipyridamole, picotamide, indobufen, anagrelide, triflusal).Aspirin (ASA) at doses up to 100 mg/day is permitted. ;* Symptomatic congestive heart failure, unstable angina pectoris, or symptomatic or poorly controlled cardiac arrhythmia. ;* Any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to randomization. ;* Uncontrolled arterial hypertension * 150 / * 90 mm Hg despite standard medical management. ;* Grade 3-4 gastrointestinal bleeding or any variceal bleeding episode in the 3 months prior to randomization requiring transfusion, endoscopic or operative intervention (patients with any bleeding episode considered life-threatening during the 3 months prior to randomization are excluded, regardless of transfusion or intervention status). ;* Esophageal or gastric varices that require immediate intervention (eg, banding, sclerotherapy) or represent a high bleeding risk. Patients with evidence of portal hypertension (including splenomegaly) or any prior history of variceal bleeding must have had endoscopic evaluation within the 3 months immediately prior to randomization. Patients with evidence of portal hypertension are eligible for study participation if endoscopic evaluation does not indicate esophageal or gastric varices that require immediate intervention or represent a high bleeding risk; however, these eligible patients must receive supportive therapy (eg, beta blocker therapy) according to institutional standards and clinical guidelines during study participation. ;* Central nervous system (CNS) metastases or carcinomatous meningitis. ;* Exclude patients with Child-Pugh Class B score.;*The study (Ramucirumab or placebo) should be discontinued in patiens with new occurrence of hepatic encephalopathy and/or hepatorenal syndrome. Following discontinuation of study drug for either of these 2 reasons, retreatment with study drug will not be permitted.

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):	12-06-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ramucirumab
Generic name:	nvt

Ethics review

Approved WMO Date:	23-12-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2014
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	EUCTR2010-019318-26-NL
ClinicalTrials.gov	NCT01140347
CCMO	NL37954.018.11