A Phase I open label/ Phase II randomized, double-blind, multicenter study investigating the combination of RAD001 and sorafenib (Nexavar®) in patients with advanced hepatocellular carcinoma

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Phase I- To characterize the safety and tolerability and determine the maximum tolerated dose of daily RAD001 in combination with daily sorafenibPhase II- To estimate the hazard ratio of the treatment effect as measure of anti-tumor activity of the...

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

Summary

ID

NL-OMON32745

Source
ToetsingOnline

Brief title
Fase I/II study: RAD001-sorafenib combination in patients with advanced hcc

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
Hepatocellular carcinoma, liver cancer

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: everolimus, hepatocellular carcinoma, RAD001, sorafenib

Outcome measures

Primary outcome

Phase I

Dose Limiting Toxicities (DLT) of treatment combination of RAD001 plus

sorafenib

Pharmacokinetic measures of systemic exposure, such as AUC, Cmax and trough

blood levels.

Both Phase I and II

efficacy evaluation based on the overall response rate according to RECIST

Secondary outcome

- clinical efficacy in terms of : objective response rate (ORR); disease

control rate (DCR); progression-free survival (PFS), according to RECIST

- safety and tolerability: rate and severity of adverse events

Study description

Background summary

Hepatocellular Carcinoma (HCC) is the 5th most common solid tumor worldwide.
Overall mortality from HCC is high with almost 600,000 deaths worldwide in 2002.
Although various chemotherapy regimens are available based on doxorubicin,

cisplatin or fluorouracil, traditionally, chemotherapy is not considered an effective treatment scheme for HCC as these tumor are chemoresistent: chemotherapy response rates of 10% can be seen with single agents and up to 20% response rates with combination based regimens.
The medical need is high for better systemic therapy for advanced HCC and the limited efficacy of the currently available drug therapies in this population despite the approval of sorafenib (received registration in the European Union for the treatment of HCC in 2007)
Mechanism of action of RAD001: the mTOR pathway has been reported to be activated in 15% to 41% of the cases and mTOR inhibitors (RAD001) show antineoplastic activity in HCC models. A combination therapy of RAD001 with sorafenibwhich will target both primary and secondary pathways may be more effective in enhancing cytotoxicity or cytostatic activity, overcoming possible resistance and limiting toxicity.

Study objective

Phase I
- To characterize the safety and tolerability and determine the maximum tolerated dose of daily RAD001 in combination with daily sorafenib
Phase II
- To estimate the hazard ratio of the treatment effect as measure of anti-tumor activity of the combination therapy at the maximum tolerated dose-level, as compared to sorafenib alone
Secundary
Phase I
- To describe any responses: CR, PR, SD, PFS, TTP, time to response, duration of response
- To characterize the pharmacokinetic (PK) profiles
Phase II
- To describe the clinical efficacy of all study treatments at 24 weeks in terms of : objective response rate (ORR); disease control rate (DCR); progression-free survival (PFS)
- To assess the safety and tolerability of RAD001 when combined with sorafenib as measured by rate and severity of adverse events
- To characterize the PK profile of RAD001 when combined with sorafenib
- To evaluate the drug-drug interaction between RAD001 and sorafenib
Plus numerous exploratory objectives

Study design

This is a combined Phase I and Phase II study and each Phase has a Core and an Extension part of the study. The Core Phase for both Phase I & Phase II consists of 24 weeks of treatment.
* Phase I Core
Phase I is an open-label, non-randomized, multi-center, designed as a

sequential dose-escalation study combining daily RAD001 plus daily sorafenib, after which phase II will be initiated in sequence
* Phase II Core
Phase II is a randomized, double-blind, parallel, two-arm multi-center study.
Randomisation over treatment arms:
1. Sorafenib 400 mg BID + RAD001 (at the phase 1 MTD dose-level)
2. Sorafenib 400 mg BID + placebo to RAD001

Once assigned to one of the 2 treatment arms the patient will be assigned, within that arm, to one of the 2 drug run-ins:
* 8 day run-in with sorafenib 400 mg BID then sorafenib 400 mg BID + RAD001/placebo
* 8 day run-in with RAD001/placebo then sorafenib 400 mg BID + RAD001/placebo
Randomized in a 1:1 ratio for a total of 40 patients per treatment arm.
* Extension part of Phase I and Phase II
Following completion of 24 weeks of treatment or early discontinuation all patients may continue to receive RAD001 along with sorafenib or alone, until progressive disease or unacceptable toxicity occurs.

Intervention

treatment with Sorafenib 400 mg BID + RAD001 (at the phase I MTD dose-level) or Sorafenib 400 mg BID + placebo. Phase I starting dose for dose finding is RAD001 2.5 mg p.o. daily.

Study burden and risks

- every potential side effect of RAD001 and/or Sorafenib
- Physical examinations including vital signs, standard MRI / CT scans, ECG, blood for PK assessment, regular monitoring of hematology (including coagulation parameters), blood chemistry, serum/urine pregnancy, blood biomarkers, and urinalyses

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

- Male or female patients * 18 years old with ability to take oral drugs
- Diagnosis of advanced HCC according to the AASLD Guidelines (Bruix and Sherman 2005)
- HCC stage B or C according to the Barcelona Clinic Liver Cancer (BCLC)
- No previous systemic therapy for HCC
- Measurable disease as per RECIST, that is, at least one lesion that has not been previously treated with local therapy. Previously treated lesions will be considered *non target* lesion. Local therapy must be completed at least four weeks prior to baseline scans.
- Patients with ECOG performance status of 0 or 1
- Cirrhotic status of current Child-Pugh class A only (5-6 points) with no encephalopathy. Child-Pugh status should be calculated based on clinical findings and laboratory results during screening period.

Exclusion criteria

- Patients currently receiving any anti cancer therapy or who have received any local anti cancer therapy *4 weeks prior to study treatment start
- Active bleeding during the last 30 days
- Known previous/current malignancy * 3 years except for cervical carcinoma in situ, basal cell carcinoma, superficial bladder carcinoma
- Known central nervous system disease
- Known history of HIV seropositivity (HIV testing is not mandatory)
- Any severe and/or uncontrolled medical conditions.

- Patients receiving chronic treatment with any systemic immunosuppressive agent

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-12-2008
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Nexavar
Generic name:	sorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog niet geregistreerd voor deze indicatie
Generic name:	everolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	06-10-2008

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2010
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	EUCTR2008-004096-21-NL
CCMO	NL25143.018.08