Fase I/II study: RAD001 and sorafenib combination in patients with advanced hcc.

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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...

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON24345

Bron
NTR

Verkorte titel
N/A

Aandoening

hepatocellular carcinoma
RAD001
sorafenib
everolimus
Leverkanker
RAD001
sorafenib
everolimus

Ondersteuning

Primaire sponsor: Novartis Pharma
Overige ondersteuning: Novartis Pharma

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Phase I:
1. Dose Limiting Toxicities (DLT) of treatment combination of RAD001 plus sorafenib;
2. 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.

Toelichting onderzoek

Achtergrond van het onderzoek

Design:
Combined Phase I (open-label, designed as a sequential dose-escalation study combining daily RAD001 plus daily sorafenib)and Phase II (randomized, double-blind) trial

Subjects:
patients with advanced hepatocellular carcinoma.

Study medication:
Sorafenib 400 mg BID + RAD001 (at the phase 1 MTD dose-level)

Clinical Phase:
Combined phase I and phase II

Objectives:
Phase 1: Evaluate the safety and tolerability of RAD001 in combination with sorafenib in patients with advance hepatocellular cancer (HCC) and to determine the maximum tolerated dose (MTD).

Phase 2: To estimate the treatment effect as a measure of anti-tumor activity in terms of Time to Progression (TTP) of the combination of RAD001 plus sorafenib, at the MTD, as compared to sorafenib alone.

Primary efficacy variable:

1. Phase I: Dose Limiting Toxicities (DLT) of treatment combination of RAD001 plus sorafenib;

A. Pharmacokinetic measures of systemic exposure, such as AUC, Cmax and trough blood levels.

2. Both Phase I and II: efficacy evaluation based on the overall response rate according to RECIST.

Secondary efficacy variables:

1. Clinical efficacy in terms of: objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), according to RECIST.

2. Safety and tolerability: rate and severity of adverse events.

Doel van het onderzoek

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.

Onderzoeksopzet

Phase I will be cohort driven with evaluation timepoints after 28 days of treatment.
In phase II evaluation will be eventdriven. (time to progression).

Onderzoeksproduct en/of interventie

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 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.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Male or female patients ¡Ý 18 years old with ability to take oral drugs;

2. Diagnosis of advanced HCC according to the AASLD Guidelines (Bruix and Sherman 2005);

3. HCC stage B or C according to the Barcelona Clinic Liver Cancer (BCLC);

4. No previous systemic therapy for HCC;

5. 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;

6. Patients with ECOG performance status of 0 or 1;

7. 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.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Patients currently receiving any anti cancer therapy or who have received any local anti cancer therapy ¡Ü4 weeks prior to study treatment start;

2. Active bleeding during the last 30 days;

3. Known previous/current malignancy ¡Ü 3 years except for cervical carcinoma in situ, basal cell carcinoma, superficial bladder carcinoma;

4. Known central nervous system disease;

5. Known history of HIV seropositivity (HIV testing is not mandatory);

6. Any severe and/or uncontrolled medical conditions;

7. Patients receiving chronic treatment with any systemic immunosuppressive agent.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd
Blindering:	Dubbelblind
Controle:	Geneesmiddel

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	01-01-2009
Aantal proefpersonen:	130
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	17-03-2009
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1631
NTR-old	NTR1728
Ander register	Novartis Pharma : CRAD001O2101
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten
N/A