An open label, stratified, single-arm phase II study of RAD001 in patients with advanced pancreatic neuroendocrine tumor (NET) after failure of cytotoxic chemotherapy

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To determine the objective response rate (ORR) (complete response and partialresponse) of RAD001 10 mg po qd monotherapy in patients with advanced(unresectable or metastatic) pancreatic NET after the failure of cytotoxicchemotherapy.

Ethical review	Approved WMO
Status	Pending
Health condition type	Neoplastic and ectopic endocrinopathies
Study type	Interventional

Summary

ID

NL-OMON29869

Source
ToetsingOnline

Brief title
Phase II study in patients with pancreas NET

Condition

- Neoplastic and ectopic endocrinopathies
- Endocrine neoplasms malignant and unspecified

Synonym
advanced islet cell carcinoma, advanced pancreatic neuroendocrine tumor

Research involving
Human

Sponsors and support

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

Intervention

Keyword: pancreatic neuroendocrine tumor, RAD001

Outcome measures

Primary outcome

objective response rate (ORR) (complete response and partial response) of RAD001 10 mg po qd monotherapy in patients with advanced (unresectable or metastatic) pancreatic NET after the failure of cytotoxic chemotherapy (stratum 1).

Secondary outcome

- duration of response to RAD001 monotherapy (stratum 1).

- objective response rate (ORR) and response duration of RAD001 10 mg po qd in patients whose tumors have progressed while receiving prior Sandostatin LAR® Depot therapy and after the failure of cytotoxic chemotherapy (stratum 2).

- safety and tolerability of RAD001 monotherapy (10 mg/d) in patients with pancreatic NET (stratum 1).

- safety and tolerability of the combination of RAD001 10 mg/d plus Sandostatin LAR® Depot in patients with pancreatic NET (stratum 2).

- progression free survival (PFS) and the overall survival (OS) of patients

receiving RAD001 10 mg per day monotherapy and of patients receiving RAD001 10

mg per day in combination with Sandostatin LAR® Depot.

- steady state exposure to RAD001 and to estimate the effect of coadministering

Sandostatin LAR® Depot on RAD001 exposure.

- effects of RAD001 on plasma angiogenic molecules such as VEGF and basic FGF.

- effects of RAD001 on serum Lactate Dehydrogenase (LDH) isozymes.

- characterize pre-treatment tumor samples by immunohistochemical and genetic

analyses indicating activation of the mTOR pathway.

- change in octreotide levels after treatment with RAD001.

- relationship between RAD001 steady state levels, tumor response, and

Chromogranin A response (50% decrease).

Study description

Background summary

RAD001 has been evaluated in phase 1 studies involving 147 patients with advanced cancers using both a weekly regimen (up to 70mg/wk) and a daily regimen (10mg/d). The adverse events are mild-moderate (CTC grade 1-2) in the majority of patients.

The dose and schedule of 10mg p.o. q.d has been selected for most phase 2 studies based on assessment of both pharmacodynamic and safety studies. Conventional cytotoxic agents were empirically evaluated in in vitro and in vivo pharmacology studies as combination partners for RAD001 and have shown that RAD001 is additive or synergistic in combination with other anticancer agents, including cytotoxics and other signal transduction inhibitors (STIs) as well as endocrine therapy. In many cases, a potentiation of cell death by the drug combination was observed.

In pancreatic NET cells, mTOR is activated in response to signaling by insulin-like growth factor 1 (IGF-1). Interruption of this signaling pathway through treatment with RAD001 in combination with a somatostatin analogue was the goal of a recent phase 2 clinical trial conducted by J. Yao at the MD Anderson Cancer
Center. Of the thirty treated patients, twenty-seven patients were evaluable for response. Four patients were reported to have partial response, 17 with stable disease (SD), and 3 with progressive disease (PD) per RECIST. Responses appeared to be durable.

Study objective

To determine the objective response rate (ORR) (complete response and partial response) of RAD001 10 mg po qd monotherapy in patients with advanced (unresectable or metastatic) pancreatic NET after the failure of cytotoxic chemotherapy.

Study design

This is a stratified two-stage, single-arm, phase 2 study of treatment with RAD001 in patients with advanced (unresectable or metastatic) pancreatic neuroendocrine
tumor (NET) after failure of cytotoxic chemotherapy.

Patients are stratified according to whether they are receiving chronic treatment with Sandostatin LAR® Depot (octreotide acetate for injectable suspension).
- Stratum 1, consisting of patients not receiving chronic Sandostatin LAR® Depot therapy, will receive RAD001 monotherapy at 10 mg/day.
- Stratum 2, consisting of patients with tumors that have progressed during Sandostatin LAR® Depot treatment will continue their entry dose of Sandostatin LAR® Depot plus RAD001 10 mg/day.

In each of the two strata, a two-stage Simon design is used allowing for early stopping after stage 1 for lack of activity. If activity is demonstrated after stage 2,
further patients will be included in a 3rd stage to increase the sample size to

100
patients in stratum 1.

All patients will be treated with RAD001 until tumor progression is documented per RECIST criteria, until unacceptable toxicity occurs, or until patient or investigator requests discontinuation of treatment.

Intervention

In stratum 1 RAD001 will be given at 10 mg po qd by continuous daily dosing until
tumor progression.

In stratum 2 patients will receive RAD001 10 mg po qd and will continue their entry
dose of Sandostatin LAR® Depot, both drugs continued until tumor progression.

Study burden and risks

Toxicity of RAD001 alone or of the combination of RAD001 and Sandostatine LAR.
Radiation exposure of CT-scans.

Contacts

Public
Novartis

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Advanced (unresectable or metastatic) biopsy-proven pancreatic neuroendocrine tumor.
* Pancreatic neuroendocrine tumor with documented objective progression of disease while receiving cytotoxic chemotherapy or documented progression at any time after receiving an adequate course of cytotoxic chemotherapy
* At screening a CT or MRI scan must demonstrate measurable disease
* Adequate liver function: bilirubin <= 1.5 x ULN; ALT and AST <= 2.5x ULN (<= 5x ULN in patients with liver metastases).
* Stratum 1: Not receiving Sandostatin LAR <= 30 days of enrollment
* Stratum 2 only: receiving treatment (at least 3 consecutive months) with Sandostatin LAR Depot.

Exclusion criteria

* Anticancer therapy within 3 weeks of enrollment
* Hepatic artery embolization within the last 6 months, or cryoablation of hepatic metastasis within 2 months of enrollment.
* Prior therapy with RAD001 (everolimus) or other rapamycins
* Uncontrolled diabetes
* Chronic active or persistent liver disease

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2006
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ng niet geregistreerd voor deze indicatie
Generic name:	Everolimus
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sandostatine LAR Depot
Generic name:	octreotide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-06-2006
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-02-2007
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2006-001247-64-NL
Other	NA
CCMO	NL12250.042.06