A phase II study to investigate the efficacy of RAD001 (Afinitor ®, everolimus) in patients with irresectable recurrent or metastatic differentiated, undifferentiated (anaplastic) and medullary thyroid carcinoma

Published: 15-02-2010
Last updated: 02-05-2024

Primary objective: To determine the efficacy of RAD001 in patients with progressive irresectable recurrent or metastatic differentiated thyroid carcinoma Secondary objectives:- To determine maximum percentage of tumor reduction-To describe activity...

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

Summary

ID

NL-OMON35047

Source
ToetsingOnline

Brief title
THYRRAD

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
thyroid cancer

Research involving

Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Novartis

Intervention

Keyword: RAD001, Thyroid cancer

Outcome measures

Primary outcome

Primary endpoint:

-Objective Response Rate according to RECIST version 1.1 in patients with progressive metastases or inoperable recurrent disease of differentiated thyroid cancer

Secondary outcome

Secondary endpoints:

-Maximum percentage of tumor reduction for target lesions (waterfall plot)

-Progression-free survival and overall survival (time to event)

-Toxicity and serious adverse events according to NCI Common Terminology Criteria for Adverse Events Version 4.0

-Evolution of serum thyroglobulin (Tg) during treatment

-Explorative pharmacogenomic, pharmacokinetic and translational studies

-Objective response rates according to RECIST version 1.1 of RAD001 in patients with progressive metastases or inoperable recurrent disease of undifferentiated (anaplastic) or medullary thyroid cancer

Study description

Background summary

Recent studies have shown the involvement of the mTOR kinase in thyroid follicular cells. mTOR inhibitors have a distinct mechanism of action from the VEGF pathway inhibitors such as VEGFR tyrosine kinase inhibitors (sunitinib and sorafenib) and VEGF ligand antibodies (bevacizumab). Therefore, resistance to VEGF inhibitors does not imply resistance to mTOR inhibitors and mTOR targeted strategies may offer new perspectives for treatment. Our study will be the first to investigate the efficacy of RAD001 (Afinitor®, everolimus) in patients with progressive irresectable recurrent or metastatic differentiated thyroid carcinoma. Furthermore, patients with progressive metastases or inoperable recurrent disease of undifferentiated (anaplastic) or medullary thyroid cancer will also have the opportunity to participate in this study, since there is a lack of therapeutic options for these patients. The primary endpoint is objective response rate according to RECIST. Secondary endpoints are maximum percentage of tumor reduction for target lesions, progression-free survival and overall survival, toxicity, evolution of serum thyroglobulin (Tg) and in addition, we will perform explorative pharmacokinetic, pharmacogenomic and translational research studies.

Study objective

Primary objective:
To determine the efficacy of RAD001 in patients with progressive irresectable recurrent or metastatic differentiated thyroid carcinoma

Secondary objectives:
-To determine maximum percentage of tumor reduction
-To describe activity time to event endpoints
-To assess toxicity
-To determine evolution of serum thyroglobulin (Tg)
-To perform explorative pharmacogenomic, pharmacokinetic and translational studies
-To investigate efficacy of RAD001 in patients with progressive metastases or inoperable recurrent disease of undifferentiated (anaplastic) or medullary thyroid cancer

Study design

Non-randomized, open-label, single arm phase II study

Intervention

RAD001 is taken orally 10 mg once daily, continuously dosed. A treatment cycle will be considered 28 days. RAD001 is formulated as tablets of either 5 mg or 10 mg strengths for oral administration.

Study burden and risks

All patients should be screened for inclusion and exclusion criteria within 4 weeks prior to the first dose of RAD001. Baseline evaluations include CT/MRI-scans, bone scan or X-rays and lab-investigations. Patients will be asked to visit the clinic monthly with the exception of day 1 and 15 of the first cycle when patients will have venapunctures before intake of RAD001 and 1, 2, and 3 hours after.

All patients will be treated with RAD001 at a once daily oral dose of 10 mg until either:
* Tumor progression determined by the investigator according to RECIST criteria
* Unacceptable toxicity
* Death
* Discontinuation from the study for any other reason

Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment. End of Treatment evaluations are to be completed whenever the patient discontinues study treatment, regardless of when it occurs. Following discontinuation of RAD001, all patients will be followed for survival for 28 days.

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

Inclusion Criteria:
* Age > 18 years
* Karnofsky performance score > 70%
* Patients with differentiated thyroid carcinoma (i.e. papillary and follicular carcinomas)
* Patients must have undergone total thyroidectomy (and having received thyrosuppressive therapy afterwards)
* Patients with no RaI uptake in tumor as proven by RaI scintigraphy performed after prior RaI therapy
* Patients with insufficient RaI uptake as proven by progression of lesions despite accumulation of RaI
* Patients with a maximum cumulative dosis of RaI
* The patient has documented progressive disease (PD) on computerized tomography (CT), magnetic resonance imaging (MRI), bone scan or X-ray, per RECIST v1.1 at screening compared with a previous image done within 14 months of screening
* The subject has no other diagnosis of malignancy (unless non-melanoma skin cancer, carcinoma in situ of the cervix, or a malignancy diagnosed * 2 years previously) and currently has no evidence of malignancy (unless non-melanoma skin cancer or carcinoma in situ of the cervix).
* Patients with history of brain metastasis who are neurologically stable following definitive radiation and/or surgery and do not require corticosteroids will be permitted.;Laboratory Requirements - within 14 days prior to enrollment:
* Patients with adequate bone marrow function defined as ANC * 1.5 x 109/L, Platelets * 100 x 109/L, Hb * 5.6 mmol/L
* Patients with adequate liver function defined as serum bilirubin * 1.5 x ULN, ALT and AST * 2.5x ULN. Patients with known liver metastases are allowed to have an AST and ALT * 5x ULN.
* Patients with adequate renal function defined as serum creatinine * 2 x ULN.
* Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to the first dose of study drug.;Additional inclusion groups

Patients with progressive metastases or inoperable recurrent disease of undifferentiated (anaplastic) or medullary thyroid cancer will also have the opportunity to participate in this study, since there is a lack of therapeutic options for these patients. The same inclusion and exclusion criteria will be used, apart from the criteria on RaI therapy, since this is not applicable for undifferentiated or medullary thyroid cancer. We will analyse these patients as separate cohorts. Patients with undifferentiated or medullary thyroid cancer will be treated and evaluated according to the same criteria as the patients included with differentiated thyroid cancer. A minimum of 7 undifferentiated thyroid cancer patients and 7 medullary thyroid cancer patients will be analysed for response rate; if no responses are found in these patient groups, further investigation of RAD001 in undifferentiated or medullary thyroid cancer patients is not warranted.

Exclusion criteria

Exclusion Criteria:
* Patients receiving chemotherapy, immunotherapy, radiation therapy or any other investigational agent within 4 weeks of the first dose of study drug, or sunitinib and/or sorafenib within 2 weeks of the first dose of RAD001. Patients must have recovered from effects of prior therapy.
* Patients who have previously received RAD001 or other mTOR inhibitors.
* Patients with known hypersensitivity to RAD001 or other rapamycin analogs (sirolimus, temsirolimus), or to its excipients.
* Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent (except corticosteroids with a daily dosage equivalent to prednisone * 20 mg for adrenal insufficiency). Patients receiving corticosteroids must be on a stable dose for * 4 weeks prior to the first dose of RAD001. Topical or inhaled corticosteroids are permitted.
* Patients with an active bleeding diathesis.
* Patients who have undergone major surgery within 4 weeks prior to starting study drug (e.g., intra-thoracic, intra-abdominal, or intra-pelvic), open biopsy, or significant traumatic injury, or who have not recovered from the side effects of any of the above.
* Patients with any severe and/or uncontrolled medical conditions such as unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction * 6 months, serious uncontrolled cardiac arrhythmia, uncontrolled hyperlipidemia, active or uncontrolled severe infection, cirrhosis, chronic or persistent active hepatitis or severely impaired lung function.
* Uncontrolled diabetes
* Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not willing to use effective birth control methods.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-04-2010
Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	everolimus
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-02-2010
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	14-04-2010
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2009-016669-27-NL
CCMO	NL31245.058.10
Other	Zal nog worden aangemeld voor www.clintrials.gov