A randomized, double-blind, multi-center phase III study comparing everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in patients with advanced gastric cancer after progression on prior systemic chemotherapy

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To compare overall survival between RAD001+BSC and placebo+BSC in patients with advanced gastric cancer after progression on prior systemic chemotherapy.

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

Summary

ID

NL-OMON35532

Source
ToetsingOnline

Brief title
Everolimus (RA001) in patients with advanced gastric carcinoma.

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Gastric carcinoma / Gastric cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: advanced Gastric cancer, Everolimus, RAD001

Outcome measures

Primary outcome

The primary endpoint of this study is overall survival (OS), defined as the

time from date of randomization to date of death due to any cause. If death has

not been observed at the date of the analysis cutoff then OS will be censored

at the date of the last contact.

Secondary outcome

The secondary efficacy objectives were to compare RAD001 against placebo with

respect to progression-free survival (PFS), quality of life, and time to

definitive deterioration in the ECOG PS scale.

A hierarchical testing strategy will be adopted in this study. PFS will be

compared between the two treatment arms provided the primary endpoint

Study description

Background summary

Currently, there is no established standard of care for the treatment of gastric carcinoma. Surgery, which is the only curative option, is effective only when performed on patients in the earliest stages of the disease. The majority of patients present with more advanced disease (inoperable or

metastatic gastric cancer) and do not qualify for surgery. First-line therapy varies but typically consists of regimens combining 5-FU and its derivatives with taxanes, platinum-based drugs, or irinotecan. Irrespective of the treatment received, survival is limited (with 5-year survival of around 20%) and a need for second and third line treatment is needed.
There is a medical need for better therapy for advanced gastric. RAD001 has a potential to act directly on the tumor cells by inhibiting tumor cell growth anad proliferation. On the other hand RAD001 has also a potential to act indirectly by inhibiting angiogenesis leading to reduced tumor vascularity.
Phase II data show a 54.7% disease control rate in Japanese patients receiving everolimus monotherapy for advanced gastric cancer after one or two prior chemotherapy regimens

Study objective

To compare overall survival between RAD001+BSC and placebo+BSC in patients with advanced gastric cancer after progression on prior systemic chemotherapy.

Study design

This is a phase III, double blind, randomized, international study comparing treatment of RAD001 plus best supportive care (BSC) against treatment with matching placebo plus BSC in patients with advanced gastric cancer who have progressed after one or two prior chemotherapy regimens for advanced disease. Patients will be randomized to receive either RAD001 or placebo; randomization will be unbalanced, 2:1 in favor of RAD001. Given the regional differences in management of Advanced Gastric Carcinoma (AGC) and the known association between performance status and outcomes in AGC, patients will be stratified by number of prior chemotherapy regimens for advanced disease and region (Asia versus Rest of World).
Study treatment will be continued until progression or intolerable toxicity. After progression, patients will continue to be followed for survival every three months till death or until study completion. If at either the interim or the final analysis, the superiority of RAD001 is demonstrated, the trial will be stopped and all available data will be reviewed by the Study Steering Committee. A decision may be made to offer RAD001 to patients on placebo at that time.

Intervention

RAD001 plus best supportive care versus placebo plus best supportive care
Best supportive care will be provided to all patients in accordance with the local practices of a
given institution or center. Best supportive care cannot contain any anti-cancer treatments.

Study burden and risks

Toxicity of RAD001 (everolimus). Radiation exposure of CT-scans.
Obtaining blood samples may cause some discomfort, bruising, bleeding from the site of sampling, formation of a blood clot, and, in rare cases, infection.

Contacts

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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

- Histologically or cytologically confirmed and documented gastric adenocarcinoma.
- Progression after 1 or 2 prior systemic chemotherapy treatments for advanced disease. Prior adjuvant/neoadjuvant therapy is allowed.
- ECOG performance status of * 2

- Patients with the following laboratory parameters:
* Absolute neutrophil count * 1.5 x 109/L
* Platelets * 100 x 109/L
* Hemoglobin (Hgb) * 4.9 mmol/L
* INR * 2.0
* Serum creatinine * 2 x Upper Limit of Normal (ULN)
* Adequate liver function (no evidence of liver metastasis: ALT and AST * 2.5 x ULN and with liver metastases: ALT and AST * 5.0 x ULN)
* Serum bilirubin * 1.5 ULN (Upper Limit of Normal)
* Normal serum calcium and serum potassium

Exclusion criteria

- Patients who have received > 2 prior systemic therapies for advanced disease. Note: If recurrence occurred during or * 24 weeks after adjuvant/neoadjuvant therapy the adjuvant/neoadjuvant therapy will be considered as one prior regimen of systemic chemotherapy.
- Administration of anti-cancer therapy within 3 weeks prior to randomization
- Known hypersensitivity to RAD001 (everolimus) or to other rapamycins
- Chronic treatment with steroids
- Major surgery * 2 weeks prior to randomization
- Malignant ascites requiring invasive therapy
- Lack of resolution of all acute toxic effects (excluding alopecia) of prior chemotherapy, radiotherapy, or surgical procedure CTC grade * 1 except neuropathy with grade 2 or less and alopecia.
- Central nervous system metastases
- Active, bleeding diathesis, or on oral anti-vitamin K medication (except low dose warfarin and acetylsalicylic acid (as long asINR is * 2.0)
- Any malignancy within 3 years of randomization (except in situ carcinoma of cervix, basal or squamous cell carcinoma)
- Any severe and/or uncontrolled medical conditions such as:
* Unstable cardiac disease
* Uncontrolled diabetes
* Acute and chronic, uncontrolled active infectious disorders and nonmalignant medical illnesses
* Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drugs, with the exception of prior gastrectomy (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome).
Note: Data from the phase II Japanese study of RAD001 in AGC does not show that gastrectomy impairs the absorption of RAD001.
* Active skin, mucosa, ocular or GI disorders of Grade > 1
* Chronic obstructive or restrictive pulmonary disease including dyspnea at rest from any cause
- Patients who are enterally fed

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:	Pending
Start date (anticipated):	18-06-2009
Enrollment:	8
Type:	Anticipated

Medical products/devices used

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:	18-05-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2010
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	EUCTR2008-00654420-NL
CCMO	NL27725.018.09