A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy

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To evaluate efficacy and safety of regorafenib in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapies.The primary efficacy endpoint of this study is * Overall survivalThe secondary efficacy endpoints of this...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON34893

Source
ToetsingOnline

Brief title
CORRECT

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
colon cancer, Colorectal cancer

Research involving

Human

Sponsors and support

Primary sponsor: Bayer
Source(s) of monetary or material Support: Bayer Healthcare AG

Intervention

Keyword: Colorectal cancer, Regorafenib

Outcome measures

Primary outcome

The primary efficacy endpoint of this study is Overall survival.

Secondary outcome

The secondary efficacy endpoints of this study are:

* Progression free survival

* Objective tumor response rate

* Disease control rate

Study description

Background summary

Unresectable metastatic CRC is not curable with currently available therapy. Several drugs including fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and anti EGFR antibodies, either given in combination or as monotherapy, have demonstrated to improve outcomes. However there are no standard management recommendations beyond these therapies to treat patients with colorectal cancer. Thus there is an unmet medical need for therapy that will prolong survival, both overall and progression-free, and control symptoms in patients who have failed several lines of treatment.

Study objective

To evaluate efficacy and safety of regorafenib in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapies.

The primary efficacy endpoint of this study is
* Overall survival
The secondary efficacy endpoints of this study are:
* Progression free survival
* Objective tumor response rate
* Disease control rate
The tertiary endpoints of this study are:
* Duration of response and stable disease
* Health Related Quality of Life
* Pharmacokinetics of regorafenib
* Biomarker evaluation

Study design

Randomized, double-blind, multi-center phase III study. Approximately 690 patients will be randomly assigned (2:1 ratio) to one of the following treatment groups:
* Regorafenib 160 mg od po. 3 weeks on/1 week off plus BSC
* Placebo plus BSC
Randomization will be stratified by
* prior treatment with VEGF targeting drugs (yes/no)
* time from diagnosis of metastatic disease (* 18 months vs < 18 months)
* geographical region (Region 1 (North America, Western EU, Israel, Australia/New Zealand) vs. Region 2 (Asia) vs. Region 3 (South America, South Africa, Turkey, Eastern EU).
In order to maintain a balanced representation of each of the three regions, Asia (Region 2) is not planned to randomize more than 250 patients.

Intervention

Approximately 690 patients will be randomly assigned (2:1 ratio) to one of the following treatment groups:
* Regorafenib 160 mg od po. 3 weeks on/1 week off plus BSC
* Placebo plus BSC

Study burden and risks

Burden:
In case of 6 cycles (6 cycles is only an example here - patients can have more cycles)
- Patient will need to visit site at least 14 times during study (7 months)
- Patient will undergo CT/MRI scans for tumor assessment (3 times extra compared to standard), bone scan and head scan when applicable (once), ECG (8 times), Echocardiography or MUGA (once plus on indication), blood sampling and urine sampling (14 times), PK blood sampling (additional 2 times), ECOG performance status (8 times), Physical examination (8 times), Pregnancy test

when applicable (once), blood pressure monitoring at home and reporting in diary (weekly first 6 weeks), Quality of Life questionnaires (7 times)
- one Safety follow-up (by phone) and survival follow-up visits
- Low fat breakfast required before study medication intake
Risks:
The main side effects of regorafenib (occurring in more than 10% of the patients) are listed below:
* Constipation
* Diarrhoea
* Hair loss (alopecia)
* Headache
* High blood pressure (hypertension)
* Increased blood levels of the pancreatic enzyme called lipase
* Inflammation of the lining the digestive tract (mucositis) and of the oral cavity (stomatitis)
* Loss of appetite
* Nausea
* Pain (e.g. in joints, muscles, abdomen, chest)
* Reduced levels of minerals in the blood including calcium, sodium and phosphorus
* Reduced numbers of red blood cells (anemia)
* Reduced numbers of virus-fighting white blood cells
* Reduced function of thyroid gland
* Shortness of breath
* Skin changes including rash, painful reddening of the skin with or without blistering, itchiness, redness, dryness and tingling and numbness of the hands and feet)
* Taste alteration
* Tiredness (fatigue)
* Voice changes/hoarseness
* Vomiting
Infrequent side effects (occurring in 5-10% of patients) include:
* Bleeding
* Dizziness
* Fever
* Impaired blood supply to the heart muscle, which may cause heart attack
* Infection, which may become severe and generalized
* Itching
* Kidney Failure
* Loss of Weight
* Reduced numbers of the cells that help the blood to clot
Side effects that have been rarely observed (single or few cases, not exceeding 5% of patients) include:
* Impaired blood supply to parts of the brain, which may cause a stroke or mini-stroke
* Dehydration
* Feeling unwell

* Transient disturbance of the liver function
* Jaundice
* Severe allergic reaction
* Reduced numbers of bacteria-fighting white blood cells
* Clots in the lung blood vessels
* Transient loss of consciousness
* Hives

Up to now, five (5) patients died of an unexpected cause while participating on regorafenib studies. The reported cases of death in these patients included heart attack, liver failure, blood clot in the lung, severe bleeding in the lungs and kidney failure. Careful assessment showed that these medical events could have been due to a number of causes, independent of the patients having received the study drug. The study doctors and independent monitoring bodies therefore felt that the potential benefits still outweighed any safety risks for other patients receiving the drug.

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

* Signed informed consent obtained before any study specific procedures. Patients must be able to understand and willing to sign a written informed consent.
* Male or female patients > 18 years of age.
* Histological or cytological documentation of adenocarcinoma of the colon or rectum.
* Progression during or within 3 months following the last administration of approved standard therapies which must include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and cetuximab or panitumumab (if KRAS WT), if approved in the respective country. A list of approved standard therapies for the respective countries is in Appendix Error! Reference source not found.. Patients who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be allowed into the study. Patients treated with oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of adjuvant therapy.
* Patients must have measurable or non measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST criteria, version 1.1).
* Eastern Cooperative Oncology Group (ECOG) Performance Status of * 1.
* Life expectancy of at least 3 months.
* Women of childbearing potential and men must agree to use adequate contraception since signing of the informed consent form until at least 3 months after the last study drug administration. The investigator or a designated associate is requested to advise the patient how to achieve an adequate birth control. Adequate contraception is defined in the study as any medically recommend method (or combination of methods) as per standard of care.
* Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting study treatment:
- Total bilirubin < 1.5 x the upper limit of normal (ULN).
- Alanine transaminase (ALT) and aspartate aminotransferase (AST) < 2.5 x ULN (<5 x ULN for patients with liver involvement of their cancer).
- Amylase and lipase < 1.5 x the ULN
- Serum creatinine < 1.5 x the ULN.
- Glomerular filtration rate (GFR) * 30 ml/min/1.73 m2 according to the MDRD (Modified diet in renal disease) abbreviated formula
- INR/PTT < 1.5 x ULN (Patients who are being therapeutically anti-coagulated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in this parameter exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.)
- Platelet count ¬> 100000 /mm3, Hemoglobin (Hb) > 9 g/dl, Absolute neutrophil count (ANC) > 1500/mm3
- Alkaline phosphatase limit < 2.5 x ULN (<5 x ULN for patients with liver involvement of their cancer)

Exclusion criteria

* Prior treatment with regorafenib.
* Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.
* Previous or concurrent cancer that is distinct in primary site or histology from colorectal cancer within 5 years prior to randomization EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors [Ta (Non invasive tumor), Tis (Carcinoma in situ) and T1 (Tumor invades lamina propria)].
* Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
* Pregnant or breast-feeding patients. Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of treatment.
* Congestive heart failure > New York Heart Association (NYHA) class 2.
* Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before start of study medication.
* Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
* Uncontrolled hypertension. (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
* Patients with phaeochromocytoma.
* Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication.
* Ongoing infection > grade 2 NCI-CTC version 3.0.
* Known history of human immunodeficiency virus (HIV) infection.
* Known history of chronic hepatitis B or C.
* Patients with seizure disorder requiring medication.
* Symptomatic metastatic brain or meningeal tumors unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry and is clinically stable with respect to the tumor at the time of study entry. Also the patient must not be undergoing acute steroid therapy or taper (chronic steroid therapy is acceptable provided that the dose is stable for one month prior to and following screening radiographic studies)
* History of organ allograft
* Patients with evidence or history of bleeding diasthesis. Any hemorrhage or bleeding event > CTCAE Grade 3 within 4 weeks of start of study medication.
* Non-healing wound, ulcer, or bone fracture.
* Renal failure requiring hemo-or peritoneal dialysis.
* Dehydration NCI-CTC version 3.0 grade > 1.
* Substance abuse, medical, psychological or social conditions that may interfere with the patient*s participation in the study or evaluation of the study results
* Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation
* Any illness or medical conditions that are unstable or could jeopardize the safety of the

patient and his/her compliance in the study.
* Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.
* Patients unable to swallow oral medications
* Persistent proteinuria of CTC Grade 3 or higher (> 3.5 g/24 hrs, measured by urine protein:creatinine ratio on a random urine sample).
* Any malabsorption condition
* Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
* Unresolved toxicity higher than NCI-CTCAE (version 3.0) Grade 1 attributed to any prior therapy/procedure excluding alopecia and oxaliplatin induced neurotoxicity *Grade 2

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:	Recruitment stopped
Start date (anticipated):	11-11-2010
Enrollment:	94
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not known yet
Generic name:	Regorafenib

Ethics review

Approved WMO Date:	26-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-10-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2011
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	EUCTR2009-12787-14-NL
CCMO	NL31465.029.10