A randomised phase II trial of imatinib alternating with;regorafenib compared to imatinib alone for the first line ;treatment of advanced gastrointestinal stromal tumour (GIST)

Published: 11-01-2016
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General aim; To dertemine if an alternating regimen of imatinib and regorafenib has sufficient activity and safety to warrant further evaluation as a first line treatment for metastatic GIST.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56311

Source
ToetsingOnline

Brief title
ALT GIST

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
gastrointestinal stromal tumour, GIST

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: Bayer,EORTC;AGITC;Bayer

Intervention

Keyword: alternating, GIST, imatinib, regorafinib

Outcome measures

Primary outcome

Objective tumour response (complete or partial response) as determinded by

RECIST v1.1 at of before 9 months

as calculated from the time from either (i) randomization (if patients have not

yet commenced treatment) or (ii) commencement of therapy (if patients are

randomized during the first cycle of imatinib) to the date of progression as

determined by RECIST v1.1

Secondary outcome

Progression free survival

Clinical benefit rate (SD + PR + CR) following 3 cycles of treatment

Time*to*treatment failure

Safety/toxicity/tolerability

Overall survival

Study description

Background summary

Despite highly active current treatment for metastatic gastrointestinal stramol tumour (GIST) with the use of imatinib, most people will ultimateli relapse amd die of multifocal metastatic disease. using an alternating regimen of imatinib

and regorafinib with brief drug free intervals may allow tumour stem cells to re-enter the cell cycle and become susceptible once more to drug therapy. Regorafenib a multi-targeted tyrosine kynase inhibitor (TKI) with activity against angiogenic, stromal and oncogenic receptor tyrosine kinases, has demonstrated activity in the treatment of GIST and is FDA approved for the third line therapy of advanced GIST.

Study objective

General aim; To dertemine if an alternating regimen of imatinib and regorafenib has sufficient activity and safety to warrant further evaluation as a first line treatment for metastatic GIST.

Study design

Prospective, randomised, open label phase II trial, with randomisation 1:1 and stratification by site, receipt of previous adjuvant therapy (prior vs none), and receipt of imatinib for metastatic disease for less than 21 days.

Intervention

Patients will be randomised to receive either:
Arm A - imatinib 400mg orally daily continuously (control arm);
Arm B - alternating 28*day periods of imatinib 400mg orally daily for 21 to 25 days followed by a washout (drug free) period of 3 to
7 days, then regorafenib 160mg orally daily for 3 weeks followed by a 7 day washout (drug free) period.
Treatment will continue until disease progression or prohibitive adverse events as detailed in the protocol.

Study burden and risks

Besides limited additional safety visits and lab investigations because of regorafenib treatment no substantial burden or risks are expectation from participation in this study for the patients.

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

1. Adults (over 18 yrs) with histologically confirmed GIST. In CD*117*negative cases DOG*1 must be positive or a KIT/PDGFRA mutation must be present., 2. Unresectable, metastatic disease., 3. No prior TKI for metastatic disease, with the exception of those patients who have had up to 21 days of uninterrupted treatment on 400mg daily of imatinib., 4. Imatinib therapy given as an adjuvant treatment and completed at least 3 months prior to entry into this trial is permitted. Patients who have progression of GIST while on adjuvant therapy are not eligible for this trial., 5. ECOG performance status 0*2, 6. Measurable disease by RECIST version 1.1. (Note: Participants with only peritoneal disease will be eligible only if they have lesions measurable in two dimensions and have at least 1 lesion, which is >= 2 cm in size)., 7. Adequate bone marrow function (Haemoglobin >= 9.0g/dL, platelet count >= 100 x 109/L, and absolute neutrophil count >= 1.5 x 109/L)., 8. Adequate liver function (Serum total bilirubin <=1.5 x ULN, INR <= 1.5, and ALT, AST, ALP <=2.5 x ULN (<= 5 x ULN for participants with liver metastases). Lipase level must be <= 1.5 x ULN., 9. Adequate renal function (Creatinine clearance > 50ml/min) based on either the Cockcroft Gault formula, 24 hour urine or Glomerular Filtration Rate (GFR scan); and serum creatinine <= 1.5 x ULN., 10. Tumour tissue available for central review., 11. Willing and able to comply with all study requirements, including treatment timing and/or nature of required assessments., 12. Study treatment both planned and able to start within 14 days of randomisation., 13.

Signed, written informed consent.

Exclusion criteria

1. Concurrent GI illness which may prevent absorption of imatinib or regorafenib - please note that prior gastrectomy or bowel resection does not exclude patients from this study., 2. Use of other investigational drugs within 4 weeks prior to enrolment., 3. Known sensitivity to any of the study drugs, study drug classes, or excipients in the formulation., 4. Participants receiving therapeutic doses of warfarin., 5. Presence of brain metastases., 6. The presence of PDGFR D842V mutation or other mutation known to cause imatinib resistance., 7. Inability to swallow tablets., 8. Arterial thrombotic or ischaemic events, such as cerebrovascular accident or pulmonary embolism within 6 months prior to randomisation; or major venous thrombotic events requiring use of an anticoagulant such as warfarin within 6 months prior to randomisation., 9. Poorly controlled hypertension (systolic blood pressure > 140 mmHg or diastolic pressure > 90 mmHg despite optimal medical management)., 10. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomisation, or non healing wound, ulcer or fracture., 11. Congestive cardiac failure (NYHA >= grade 2), unstable angina or new onset angina within the previous 3 months, or AMI within the previous 6 months. Cardiac arrhythmias requiring antiarrhythmic, therapy (beta blockers or digoxin are permitted)., 12. Haemorrhage or bleeding event >= Grade 3 according to CTCAE v4.0 within 4 weeks prior to randomisation., 13. Ongoing infection of > Grade 2 according to CTCAE v4.0., 14. Active hepatitis B or C or HIV, or chronic hepatitis B or C requiring treatment with antiviral therapy. Testing for these is not mandatory unless clinically indicated., 15. Interstitial lung disease with ongoing signs and symptoms., 16. Persistent proteinuria of >= Grade 3 (>3.5g/24 hours) according to CTCAE v4.0, 17. Other significant medical or psychiatric condition judged by the investigator to interfere with protocol requirements., 18. Use of biological response modifiers such as granulocyte colony stimulating factor (G*CSF), within 3 weeks prior to randomisation., 19. Patients taking strong cytochrome P (CYP) CYP3A4 inhibitors (eg clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinovir, telithromycin, voriconazole) or strong CYP3A4 inducers (eg carbamazepine, phenobarbitol, phenytoin, rifampicin, St John*s wort)., 20. History of another malignancy within 5 years prior to registration. Patients with a past history of adequately treated carcinoma*in*situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or superficial transitional cell carcinoma of the bladder are eligible., Patients with a history of other malignancies are eligible if they have been continuously disease free for at least 5 years after definitive primary treatment. , 21. Pregnancy, lactation, or inadequate contraception. Women must be post menopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a, negative pregnancy test done within 7 days

prior to registration. Women of childbearing potential and men must agree to use adequate contraception before entering the trial until at, least 8 weeks after the last study drug administration.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-11-2016
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	imatinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	regorafenib
Generic name:	regorafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-01-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	06-04-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-04-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2015-001298-42-NL
ClinicalTrials.gov	NCT02365441
CCMO	NL55529.031.15