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A phase II double-blind, randomised controlled trial of VEGF inhibitor axitinib monotherapy with early dynamic contrast-enhanced ultrasound monitoring in chemo-refractory third-line metastatic colorectal cancer

Submission date 25/10/2013	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol
Registration date 25/10/2013	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 24/07/2020	**Condition category** Cancer	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol
http://www.cancerresearchuk.org/cancer-help/trials/a-trial-looking-axitinib-advanced-bowel-cancer-axmus-c

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04355156

Clinical Trials Information System (CTIS)
2011-002598-49

Protocol serial number
12424

Study information

Scientific Title
A phase II double-blind, randomised controlled trial of VEGF inhibitor axitinib monotherapy with early dynamic contrast-enhanced ultrasound monitoring in chemo-refractory third-line metastatic colorectal cancer

Acronym
AXMUS-C

Study objectives
A Phase II, double-blind, two-arm pilot randomised placebo-controlled trial. 50 patients will be randomised 2:1 to Axitinib or placebo.

Main inclusion criteria: chemo-refractory third-line metastatic CRC with US-assessable liver or other abdominal metastases that can have a baseline DCEUS baseline measurement.

Arm A: Axitinib monotherapy started in all patients at 5 mg bd, and increased fortnightly by a dose level as tolerated to a maximum dose of 10 mg bd.

Arm B: Placebo at 2:1 ratio to treatment

Follow up: Optional visit at 48-72 hours post first dose for measurement of temperature, oxygen saturations, blood pressure and CEHPI. Outpatient monitoring at 2 weeks and 4 weeks post first dose and at 4-week intervals thereafter which will include medical history and examination, measurement of temperature, oxygen saturations and blood pressure, urinalysis and blood tests including GI profile and VEGF-PK samples. RECIST restaging at 8 weeks and at 8 weekly intervals thereafter. CEHPI will be performed at baseline, optionally at 48-72 hours, 2 weeks and 8 weeks for assessment of differential blood supply.

At 8 weeks, after tumour CT RECIST assessments, conventional responders (CR/PR/SD) continue monotherapy. In non-responders (PD), monotherapy can be continued if the patient chooses to continue and if tolerated.

Ethics approval required
Old ethics approval format

Ethics approval(s)
12/LO/0066; First MREC approval date 23/04/2012

Study design
Randomised interventional treatment trial

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: National Cancer Research Network; Subtopic: Colorectal Cancer; Disease: Colon, Rectum

Interventions
Arm A: Axitinib monotherapy started in all patients at 5 mg bd, and increased fortnightly by a dose level as tolerated to a maximum dose of 10 mg bd.

Arm B: Placebo at 2:1 ratio to treatment

Axitinib/ Placebo +CEPHI, Axitinib, a substituted indazole derivative, is an oral, potent, and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2 and 3

After 4 hours of fasting, a DCE-US scan is performed on each subject in the supine position using an iU22 ultrasound scanner (Philips Healthcare, Andover, MA) with a C5-1 curvilinear transducer. The probe is held still in the right intercostal space in order to visualise the porta hepatis. This allows simultaneous visualization of the hepat.

Study Entry : Single Randomisation only

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Axinitib

Primary outcome(s)
To demonstrate a progression-free survival to Axitinib monotherapy in metastatic colorectal cancer

Key secondary outcome(s))
Not provided at time of registration

Completion date
31/03/2015

Eligibility

Key inclusion criteria
Participants must meet all of the following inclusion criteria to eligible for enrollment into the trial:
1. Histologically or cytologically confirmed adenocarcinoma of the colon or rectum with liver metastas(es), at least one of which should not have had any focal therapy including

radiofrequency ablation, chemoembolization, ethanol or cryoablation.
2. Failed at least two chemotherapy regimens in advanced disease.
3. Evidence of unidimensionally measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST).
4. Male and female, 18 years of age or older.
5. ECOG performance status of 0 or 1.
6. Resolution of all acute toxic effects of prior therapy e.g. radiotherapy or surgical procedure to NCI CTCv4 grade =1.
7. Adequate organ function as defined by the following criteria:
7.1. Serum aspartate aminotransferase (AST¿ serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine aminotransferase (ALT¿ serum glutamic pyruvic transaminase [SGPT]) ≤2.5 x upper limit of normal (ULN). For patients with liver metastases, <5 x ULN.
7.2. Total serum bilirubin <1.5 x ULN
7.3. Serum albumin ≥3.0 g/dL
7.4. Absolute neutrophil count ≥1500/µL
7.5. Platelets ≥100,000/µL
7.6. Haemoglobin ≥9.0 g/dL
7.7. Serum creatinine ≤1.5 x ULN
8. Signed and dated informed consent form
9. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures
10. At least 2 weeks since the end of prior systemic treatment (4 weeks for Bevacizumab-containing regimens), radiotherapy, or surgical procedure with resolution of all treatment-related toxicity to NCI CTCAE Version 3.0 grade ≤1 or back to baseline except for alopecia or hypothyroidism.
11. No evidence of pre-existing uncontrolled hypertension as documented by two baseline blood pressure readings taken at least 1 hour apart. The baseline systolic blood pressure readings must be ≤140 mmHg, and the baseline diastolic blood pressure readings must be ≤90 mmHg. Patients whose hypertension is controlled by anti-hypertensive therapies are eligible.
12. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to treatment.
13. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrolment.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria

Participants must be excluded if they present with any of the following exclusion criteria:
1. Non-exposed to both oxaliplatin and irinotecan FP based cytotoxic chemotherapy (prior pelvic radiation therapy including adjuvant or neoadjuvant chemoradiation therapy for resected rectal cancer is allowed provided it is completed within 4 weeks prior to study entry)
2. Current use or anticipated need for treatment with drugs that are known CYP3A4 or CYP1A2 inducers (i.e., carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, and St Johns wort). Current use or anticipated need for treatment with drugs that are known CYP3A4 inhibitors (i.e., grapefruit juice, ketoconazole, nefazodone, itraconazole, miconazole, erythromycin, clarithromycin, telithromycin, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine)
3. Any of the following within the 12 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism.
4. Non-English speaking
5. Pregnancy, breastfeeding, or unwillingness/inability to employ an effective method of birth control/contraception to prevent pregnancy during treatment and for up to 3 months after discontinuing study drug if of reproductive potential.
6. Hypertension uncontrolled by medication (>150/100 mmHg despite optimal medical therapy).
7. Diagnosis of any second malignancy within the last 3 years that is potentially liable to interfere with study outcomes (basal cell carcinoma, squamous cell skin cancer, or in situ carcinoma and hormone-controlled locally advanced prostate cancer that has been adequately treated with no evidence of recurrent disease for 12 months, are allowed)
8. Prior surgery or IMP within 4 weeks prior to study entry
9. Current treatment within another therapeutic clinical trial.

Date of first enrolment
05/09/2012

Date of final enrolment
31/03/2015

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Hammersmith Hospital
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Sponsor information

Organisation
Imperial College of Science, Technology and Medicine (UK)

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Industry

Funder Name
Pfizer Ltd

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No