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FOCUS4: Molecular selection of therapy in colorectal cancer

Submission date 16/10/2013	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 16/10/2013	**Overall study status** Completed	
Last Edited 26/04/2023	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-treatments-for-different-types-of-bowel-cancer-focus4

Study website
http://www.focus4trial.org

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2012-005111-12

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
14893

Study information

Scientific Title
Molecular selection of therapy in colorectal cancer: a molecularly stratified randomised controlled trial programme

Acronym
FOCUS4

Study objectives
FOCUS4 is an umbrella, or platform, for testing novel agents in biomarker-defined subpopulations of first-line advanced disease colorectal cancer patients who are not considered candidates for potentially curative surgery. It is also a trial of a new strategy for testing stratified approaches to therapy in any biologically complex tumour type. See Trial Schema in the Trial Protocol.
The backbone of the platform is 16 weeks of treatment with any standard first line colorectal cancer treatment, after which, as is frequently standard practice in the UK and Europe, there is a programmed treatment break for responding and stable patients. During that break, either new agent(s) or placebo is administered. The primary outcome measure for assessing the activity of the new treatment is progression free survival in the interval (time to death or progression requiring resumption of chemotherapy).
At present, four coherent biomarker-stratified groups can be identified and trials will be established in each of these cohorts as follows:
- BRAF mutant
- PIK3CA mutation or complete loss of PTEN on IHC
- KRAS or NRAS mutant
- All wild type (no mutations of BRAF, PIK3CA, KRAS or NRAS)
- Unclassified biomarker results
For each of these subgroups, a relevant novel agent or combination is to be tested in an adaptive double blind randomised trial design with multiple interim analyses for early termination if there is no strong evidence of worthwhile activity (the principles are derived from the Multi-Arm, Multi-Stage (MAMS) design).

FOCUS4 will open with one molecularly stratified trial (FOCUS4-D) testing AZD8931 (a HER 1,2 3 inhibitor) against placebo in patients stratified into the All wild-type cohort. In addition, a non-stratified trial (FOCUS4-N) will be open for patients whose biomarker results are unclassified or who are unable or unwilling to participate in the molecular trial available to them. The molecularly stratified trials for the BRAF, PIK3CA, KRAS/NRAS mutant cohorts are still in development and will be updated on this site when they open. Target recruitment levels will also be adjusted at that time.

Ethics approval required
Old ethics approval format

Ethics approval(s)
MREC; 10/05/2013; 13/SC/0111

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
http://www.focus4trial.org/informationforpatients/furtherinformation

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

Interventions
AZD8931 (for FOCUS4-D), HER 1,2 3 Inhibitor; Capecitabine (FOCUS4-N), Oral 5FU pro drug
Randomisation is performed using minimisation with a random element. Minimisation factors are based upon known prognostic factors for outcome.

For FOCUS4-D: The trial medication is orally administered twice daily over a continuous 28 day cycle. Patients are followed up every 4 weeks for symptoms and toxicity when they also collect their double-blind placebo controlled prescription from hospital pharmacy. CT scans are performed every 8 weeks to determine progression status of the tumour.

For FOCUS4-N: Capecitabine is an oral administration taken twice daily for 14 days followed by a 7 day break before recommencing the 21 day cycle. All patients from both arms are required to attend an outpatients appointment every 3-4 weeks to assess symptoms and toxicity and for those in the capecitabine arm, they need to collect their next prescription. All patients have a CT scan every 8 weeks to determine progression status of the tumour.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Capecitabine, sapitinib (AZD8931), adavosertib (AZD1775)

Primary outcome measure
Progression free survival, determined by multi-stage design of each molecular trial

Secondary outcome measures

Overall survival: becomes a joint primary outcome if the trial continues to the final stage analysis

Overall study start date
01/12/2013

Completion date
30/10/2020

Eligibility

Key inclusion criteria
Registration inclusion criteria (please refer to the protocol for eligibility for randomisation)
1. Male/female patients at least 18 years old
2. Formalin fixed paraffin embedded (FFPE) tumour block taken prior to the commencement of standard chemotherapy and available for biomarker analysis
3. Histologically confirmed adenocarcinoma of the colon/rectum
4. Inoperable metastatic or locoregional disease (synchronous or metachronous)
5. WHO performance status 0, 1 or 2
6. Unidimensionally measurable disease RECIST 1.1 classification
7. Have had an electronically accessible CT scan performed within 4 weeks prior to start of standard chemotherapy
8. Platelet count < 400 x 109/L prior to start of standard chemotherapy
9. For women of childbearing potential, a negative pregnancy test and acceptable contraceptive precautions
10. Effective contraception for male patients if the risk of conception exists
11. Consent for screening of an archival FFPE tumour block for biomarker analysis (PIS1 & CF1)
13. Patients should have sufficient capacity for informed consent and provided signed informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size (based upon FOCUS4-D and FOCUS4-N being open): 384; UK Sample Size: 384; Recruitment will be updated as other trials open

Key exclusion criteria
Registration exclusion criteria (please refer to the protocol for eligibility for randomisation)
1. Previous systemic palliative chemotherapy using a different regimen for established advanced or metastatic disease
2. Adjuvant chemotherapy given in the last 6 months

3. Patients with brain metastases
4. Pregnant and lactating women

Date of first enrolment
01/12/2013

Date of final enrolment
30/11/2017

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
MRC CTU
London
United Kingdom
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Sponsor information

Organisation
The Medical Research Council (MRC) (UK)

Sponsor details
The Medical Research Council Clinical Trials Unit at UCL
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Sponsor type
Research council

ROR
https://ror.org/03x94j517

Funder(s)

Funder type
Government

Funder Name
Cancer Research UK (UK)

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Efficacy and Mechanism Evaluation Programme; Grant Codes: 11/100/50

Alternative Name(s)
NIHR Efficacy and Mechanism Evaluation Programme, EME

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The results from the primary analysis were published in September 2021 in the Journal of Clinical Oncology.

Intention to publish date
13/09/2021

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request. All requests will be reviewed by the Data Sharing Committee at the MRC CTU at UCL and by the FOCUS4 Trial Management Group.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	pre-trial inter-laboratory analytical validation results	01/01/2016		Yes	No
Results article	FOCUS4-D results	01/03/2018		Yes	No
Results article	FOCUS4-C (adavosertib) results	20/09/2021	20/09/2021	Yes	No
Results article	FOCUS4-N results for capecitabine	13/09/2021	20/09/2021	Yes	No
Other publications	editorial discussing the evidence for treatment breaks following FOCUS4-N results	13/09/2021	26/01/2022	Yes	No
HRA research summary			28/06/2023	No	No