

# FOCUS4: Molecular selection of therapy in colorectal cancer

<b>Submission date</b> 16/10/2013	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 16/10/2013	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 26/04/2023	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## 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

### Contact name

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### Contact details

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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 10<sup>9</sup>/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

WC2B 6NH

## Sponsor information

**Organisation**

The Medical Research Council (MRC) (UK)

**Sponsor details**

The Medical Research Council Clinical Trials Unit at UCL

Institute of Clinical Trials & Methodology

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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?
<a href="#">Results article</a>	pre-trial inter-laboratory analytical validation results	01/01/2016		Yes	No
<a href="#">Results article</a>	FOCUS4-D results	01/03/2018		Yes	No
<a href="#">Results article</a>	FOCUS4-C (adavosertib) results	20/09/2021	20/09/2021	Yes	No
<a href="#">Results article</a>	FOCUS4-N results for capecitabine	13/09/2021	20/09/2021	Yes	No
<a href="#">Other publications</a>	editorial discussing the evidence for treatment breaks following FOCUS4-N results	13/09/2021	26/01/2022	Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No