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# Safety and tolerability of Capecitabine and Aflibercept in patients with unresectable metastatic colorectal cancer deemed unsuitable for doublet/ triplet chemotherapy

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| **Submission date**<br>30/01/2014 | **Recruitment status**<br>No longer recruiting | [X] Prospectively registered<br>[_] Protocol |
| **Registration date**<br>30/01/2014 | **Overall study status**<br>Completed | [_] Statistical analysis plan<br>[X] Results |
| **Last Edited**<br>10/05/2021 | **Condition category**<br>Cancer | [_] Individual participant data |

**Plain English summary of protocol**
http://www.cancerresearchuk.org/about-cancer/trials/a-trial-looking-at-capecitabine-aflibercept-bowel-cancer-spread-elsewhere-in-the-body-capital

## Contact information

**Type(s)**
Scientific

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## Additional identifiers

**Clinical Trials Information System (CTIS)**
2013-002308-15

### Protocol serial number
15799

# Study information

### Scientific Title
A dose finding study evaluating the safety and tolerability of CAPecitabine and AflIbercept in patients with unresectable metasTAtic colorectaL cancer deemed unsuitable for doublet/ triplet chemotherapy

### Acronym
CAPITAL

### Study objectives
Evaluate the safety and tolerability of Capecitabine and Aflibercept in patients with unresectable metastatic colorectal cancer deemed unsuitable for doublet/ triplet chemotherapy.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
13/EE/0343; First MREC approval date 29/11/2013

### Study design
Non-randomised; Interventional; Design type: Treatment

### 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
This is a single arm multi-centre phase I/II study in patients with advanced colorectal cancer. Initially this will consist of a phase 1 dose escalation study in patients with advanced colorectal cancer whose disease has already grown despite a first course of chemotherapy. This phase will establish a recommended dose combination for the phase 2 study (RP2D).

The phase 2 study will evaluate this combination as a first line treatment in patients with metastatic colorectal cancer for whom standard doublet chemotherapy would not be deemed suitable.

Clinicians/research staff at participating research centres will review potential patients and assess their suitability for the trial. The patient must have a histologically proven colorectal cancer with evidence of metastatic disease. The clinician/research team member will then discuss the trial with the patient, who, if interested will be given a patient information sheet (PIS) to read and encouraged to ask any questions.

Once patients have consented to participate in the trial they will undergo a series of assessments and blood tests which are listed below:-

1. Full blood count and clotting screen
2. Urea and electrolytes, liver function tests (including ALP, AST or ALT, bilirubin)
3. Blood tests for serum creatinine to estimate glomerular filtration rate
4. Blood test for serum CEA tumour marker
5. Urine test
6. Echocardiogram (heart ultrasound scan)
7. Electrocardiogram (ECG)
8. CT scan of the chest, abdomen and pelvis to evaluate disease burden
9. Blood pressure measurement
10. Pregnancy test (if female and child bearing age)
11. Full medical history and current medications
12. Physical examination
13. ECOG performance status

For phase II patients nurses or dedicated research members will perform a questionnaire with the patients as part of a Comprehensive Health Assessment. This will include an assessment of other medical problems, a memory test and a questionnaire designed to assess function regarding activities of daily living. In addition to this the patients will also complete written questionnaires to assess overall quality of life.

The above information will then will used by doctors to decide if the patient meets the eligibility criteria of the trial.

Patients will also be asked if they would be willing to undergo a biopsy of their cancer for research purposes. This biopsy is purely optional and a refusal will not affect any further participation in the trial.

Once the patients have entered the trial they will receive the combination treatment. All patients will receive an IV infusion of Aflibercept (day 1) and start twice daily capecitabine tablets which they will take twice a day for 2 weeks. Each cycle is 3 weeks long and involves one week without treatment. The initial starting dose of Aflibercept is 6.5mg/kg + twice daily Capecitabine at a dose of 850mg/m2.

Before each cycle the patient will be seen by a doctor/dedicated research team member and undergo the following assessments

1. Full blood count and clotting screen
2. Urea and electrolytes, liver function tests (including ALP, AST or ALT, bilirubin)
3. Blood tests for serum creatinine to estimate glomerular filtration rate
4. Blood pressure measurement
5. Urine sample
6. Physical examination and toxicity assessment
7. ECOG performance status
8. Blood tests to assess pharmacodynamic parameters (week 1 and 3 in the first cycle)

At 12 and 24 weeks they will also have a repeat electrocardiogram (ECG) and a CT scan of the chest, abdomen and pelvis to assess disease response. For phase II patients only further questionnaires will be undertaken at 12 and 24 weeks to assess the impact of treatment on quality of life and activities of daily living.

Responses will be assessed by CT using RECIST criteria and if the patients disease is progressing they will no longer continue on the trial. Patients can also be withdrawn for toxicity reasons or if treatment is delayed for >3weeks. Following completion of the trial patients will be followed up for 28 calendar days after the last administration of the study drug. If there are adverse events that occurred while the patient was on study which are attributed (including possibly drug-related AEs) to the study drug and are still present 28 calendar days after the last administration of study drug or occur in the 28 calendar days post study drug administration; the patient will be followed up monthly afterwards until resolution or stabilisation of these events, unless the patient starts another anti-tumour treatment. Although the Investigator will make every reasonable effort to keep each patient on study until the patient progresses or receives the maximum number of cycles, the patient may be removed from the study for other reasons.

## Intervention Type
Drug

## Phase
Phase I/II

## Drug/device/biological/vaccine name(s)
Capecitabine, aflibercept

## Primary outcome(s)
Phase I, primary outcome measure:
To evaluate the maximum tolerated dose in a selected group of patients with good performance status with metastatic disease who have progressed on at least first line therapy.

Phase II, primary outcome measure:
To establish safety and tolerability of recommended phase II treatment dose of aflibercept and capecitabine in patients not suitable for doublet/triplet cytotoxic chemotherapy.

## Key secondary outcome(s))
Phase I, secondary outcome measure:
Overall response rate in this group and to evaluate the overall treatment toxicity profile in this group.

Phase II, secondary outcome measures:
To establish the overall response rate (ORR) in this group
To assess the overall treatment utility of this combination via the use of a comprehensive health assessment tool.
To evaluate the overall treatment toxicity profile according to the CTC v4.03.
To assess progression free survival in this group
To explore potential VEGF-targeted predictive biomarkers.

## Completion date
17/02/2016

# Eligibility

### Key inclusion criteria
Summary of Inclusion Criteria for both the Phase I and Phase II part of the trial:
1. Histologically confirmed colorectal cancer with evidence of metastatic disease
2. Adequate medical fitness to undergo fluoropyrimidine-based chemotherapy.
3. No known dihydropyrimidine dehydrogenase deficiency
4. Adequate bone marrow function with platelets > 100 x 10E9/l; WBC > 3 x 10E9/l; neutrophils > 1.5 x 10E9/l; Hb > 9 g/dl
5. Serum bilirubin < 1.5 x upper limit of institutional normal range (ULN), alkaline phosphatase <5x ULN and transaminases <3 x ULN unless liver metastasis then <5 x ULN
6. Serum creatinine = 1.5 x ULN or creatinine clearance >50ml/min
7. Proteinuria <2+ (dipstick urinalysis) or =1g/24hour.
8. Written informed consent
9. For female patients of childbearing potential, negative serum pregnancy test within 1 week (7 days) prior of starting study treatment
10. Female patients must commit to using reliable and appropriate methods of contraception until at least three months after the end of study treatment (when applicable). Male patients with a partner of childbearing potential must agree to use contraception in addition to having their partner use another contraceptive method during the trial.
11. Absence of pre-existing liver dysfunction of Childs-Pugh B or worse
12. Life expectancy > 3 months
13. Age = 18 years Phase I study specific criteria:
14. WHO performance status 0 - 1
15. Progressive disease after at least first line chemotherapy treatment

Phase II study specific criteria:
1. WHO performance status 0  2
2. Patients not deemed suitable for doublet/triplet combination chemotherapy. This will be defined as 2 or more moderate (grade 2) comorbidities or 1 or more severe (grade 3) on CIRSG and/or MMSE of 26 or below and or IADL impairment in more than 1 category and or physical function difficulty from physical function section of EORTC QLQC30.
3. No previous treatment for mCRC

### Participant type(s)
Patient

### Healthy volunteers allowed
No

### Age group
Adult

### Lower age limit
18 years

### Sex
All

### Key exclusion criteria

The exclusion criteria for the phase I and II part of the trial is as follows:
1. Known evidence of brain metastases
2. Liver-only metastatic disease deemed to be resectable
3. LVEF = 55%
4. Patients who did not previously tolerate IV 5FU or capecitabine (required dose reduction, significant delay (>=7 days) or stopped treatment due to fluoropyrimidine toxicity
5. Any of the following within 3 months prior to inclusion: grade 34 gastrointestinal bleeding /haemorrhage (unless due to resected tumour), treatment resistant peptic ulcer disease, erosive oesophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism or other uncontrolled thromboembolic event
6. Any of the following within 6 months prior to inclusion: myocardial infarction, acute coronary syndrome, unstable angina pectoris, coronary revascularisation (PCI or CABG), NYHA class III or IV congestive heart failure, stroke or transient ischaemic attack
7. Any patient who has undergone major surgery <1month prior to trial entry
8. Uncontrolled hypertension (grade 3 /4)
9. Significant proteinuria (=2+ on dipstick or =1g/24hour)
10. Significant bleeding diathesis or significant underlying coagulopathy (INR>1.5) in the absence of vitamin K antagonist therapy.
11. Intolerance to loperamide
12. Previous history of gastrointestinal fistula or perforation
13. Evidence of bowel obstruction
14. Clinically relevant history of drug or alcohol abuse
15. Serious uncontrolled inter current illness including poorly controlled diabetes mellitus
16. HIV, HBV or HCV infection
17. Pregnancy or lactation. Men and women of childbearing potential must use adequate contraception
18. Any psychological, familial, sociological or geographic condition potentially hampering compliance with the study protocol and follow-up schedule
19. Recovery from any treatment related grade 3/4 non-haematological toxicity (except alopecia and fatigue) to baseline or = grade 1

### Date of first enrolment
13/02/2014

### Date of final enrolment
17/02/2016

## Locations

### Countries of recruitment
United Kingdom

England

### Study participating centre

**Guy's and St Thomas' NHS Foundation Trust**
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# Sponsor information

**Organisation**
Guy's and St. Thomas' NHS Foundation trust (UK)

**ROR**
https://ror.org/00j161312

# Funder(s)

**Funder type**
Industry

**Funder Name**
Sanofi Aventis (UK)

# 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? |
|---|---|---|---|---|---|
| Results article | phase I results presented at ECCO | 01/02/2017 | 27/04/2018 | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |