

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

Submission date 30/01/2014	Recruitment status No longer recruiting	☒ Prospectively registered ☐ Protocol
Registration date 30/01/2014	Overall study status Completed	☐ Statistical analysis plan ☒ Results
Last Edited 10/05/2021	Condition category 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

Contact name

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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

Primary study design

Interventional

Study design

Non-randomised; Interventional; Design type: Treatment

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 $> 100 \times 10^9/l$; WBC $> 3 \times 10^9/l$; neutrophils $> 1.5 \times 10^9/l$; Hb > 9 g/dl
5. Serum bilirubin $< 1.5 \times$ upper limit of institutional normal range (ULN), alkaline phosphatase $< 5 \times$ ULN and transaminases $< 3 \times$ ULN unless liver metastasis then $< 5 \times$ ULN
6. Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance > 50 ml/min
7. Proteinuria $< 2+$ (dipstick urinalysis) or ≤ 1 g/24 hour.
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 3/4 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 < 1 month prior to trial entry
8. Uncontrolled hypertension (grade 3/4)
9. Significant proteinuria ($\geq 2+$ on dipstick or $\geq 1\text{g}/24\text{hour}$)
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 $\leq$ 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
London
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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