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Fluorouracil and folinic acid (FOLFIRI) plus an endothelin receptor antagonist (ERAT) in advanced colorectal cancer patients who have failed on oxaliplatin-containing chemotherapy

Submission date 03/06/2009	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 20/07/2009	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 24/07/2019	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol
http://www.cancerhelp.org.uk/trials/a-trial-looking-ZD4054-with-chemotherapy-treat-bowel-cancer-that-has-spread-FOLFERA

Study website
http://www.WCTU.org.uk

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01205711

Secondary identifying numbers
SPON671-09

Study information

Scientific Title
A randomised phase II study of Irinotecan, 5-fluorouracil and folinic acid (FOLFIRI) with or without the addition of an endothelin receptor antagonist in patients with metastatic colorectal cancer after failure of oxaliplatin-containing chemotherapy

Acronym
FOLFERA

Study objectives
The availability of agents including irinotecan, oxaliplatin, cetuximab and bevacizumab, has improved the median survival of patients with metastatic colorectal cancer (mCRC), however the prognosis remains poor. There is a need to develop other agents to improve the outcome for these patients.

Endothelin-1 (ET-1) is a potent vasoconstrictor and acts through its G-protein coupled receptors ETA (ETAR) and ETB (ETBR). ET-1 and ETAR are over-expressed in colorectal cancer and are prognostic for poor outcome. Inhibition of ETAR has been shown to enhance cytotoxicity when combined pre-clinically with chemotherapy agents such as 5-fluorouracil (5-FU), and platinums (e. g., cisplatin). ZD4054 is a specific inhibitor of ETAR.

Irinotecan is licensed for the treatment of metastatic colorectal cancer. In this study, we hypothesise that it may be possible to increase the anti-tumour activity of irinotecan and 5-FU (FOLFIRI) regimen by combining it with ZD4054.

Please note, as of 01/03/2011 the anticipated end date for this trial has been updated from 01 /09/2011 to 07/04/2012 and the target number of participants has increased from 112 to 122.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Nottingham Research Ethics Committee 2 on 13/11/2009 (ref: 09/H0408/88)

Study design
Multicentre phase II parallel group double-blind randomised controlled trial

Primary study design
Interventional

Secondary study design

Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to rquest a patient information sheet

Health condition(s) or problem(s) studied
Locally advanced and/or metastatic colorectal cancer (mCRC)

Interventions
Patients will be recruited over 18 months. Participants randomised to the control arm will receive 12 cycles (q14 days) of FOLFIRI chemotherapy: irinotecan (180 mg/m^2) administered as a two hour infusion on day 1, leucovorin (400 mg/m^2) administered as a two hour infusion on day 1, followed by a loading dose of 5-FU (400 mg/m^2) intravenous (IV) bolus administered on day 1, then 5-FU (2400 mg/m^2) administered by ambulatory pump for a period of 46 hours every two weeks. Patients will also receive the placebo tablet daily.

Participants randomised to the experimental arm will receive 12 cycles (q14 days) of the FOLFIRI regimen as outlined above with an oral daily dose of 10 mg ZD4054.

Participants, who have at least stabilisation of their disease at the end of the 24 week treatment period, may continue on their allocated ZD4054/placebo monotherapy until disease progression, unacceptable toxicity or they withdraw consent.

The following assessments will be made after the patient has consented to enter the trial:
Baseline (inclusive of eligibility screening collected after patient consent):
1. Medical history
2. Full clinical examination to evaluate measurable disease by RECIST v1.1 criteria
3. Computerised axial tomography (CT) scan of chest, abdomen and pelvis
4. Haematology, serum and urine biochemistry
5. WHO performance status
6. Pregnancy test (females of child bearing potential only)
7. Electrocardiogram (ECG)
8. Baseline toxicity
9. Collection of tumour tissue biopsy (optional for participant)

Before, during and at end of treatment (each cycle unless stated otherwise):
1. Full clinical examination to evaluate disease response by RECIST v1.1 criteria (weeks 8, 16 and 24)
2. CT scan of chest, abdomen and pelvis (weeks 8, 16 and 24)
3. Haematology and serum biochemistry
4. WHO performance status
5. Evaluation of toxicities using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0 and real-time serious adverse events (SAE) reporting
6. Documentation of dose delays and/or reduction

At Follow up (weeks 36, 48 and 60)
1. WHO performances status
2. Full clinical examination to evaluate disease response by RESIST v1.1 criteria
3. CT scan (every 12 weeks for all patients until disease progression)
4. Haematology and serum biochemistry
5. Evaluation of toxicities using NCI CTCAE v 3.0 and real-time SAE reporting

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Irinotecan, leucovorin, 5-fluorouracil (5-FU), ZD4054

Primary outcome measure
Progression free survival (PFS) at 16 weeks from the date of enrolment. This is the proportion of participants who are alive at 16 weeks without disease progression according to RECIST v1.1.

Secondary outcome measures
1. PFS (time-to-event). This is the proportion of participants who are alive at 16 weeks without disease progression according to RECIST v1.1.
2. Safety, tolerability (side effects) and feasibility of use (number of participants requiring dose delays or reductions and/or treatment withdrawal)
3. Objective response rate as assessed by RECIST v1.1
4. Overall survival (OS). Time from enrolment to death. Those still alive will be censored at time last seen.
5. To assess tumours for ETAR expression, K-ras status and alterations in relevant pathways such as MAPK/ERK and to potentially look at circulating tumour and lymphocyte cells in the blood

Overall study start date
01/09/2009

Completion date
27/06/2012

Eligibility

Key inclusion criteria
1. Histological or cytological diagnosis of metastatic colorectal cancer
2. If patients progress within 6 months of adjuvant oxaliplatin containing chemotherapy they will be included in this study providing that they have no significant ongoing toxicity (excluding grade 1 neurotoxicity)
3. Measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST v 1.1)
4. Adequate bone marrow, hepatic and renal function including the following:
4.1. Haemoglobin greater than or equal to 9.0 g/dl (no prior transfusion) or greater than or equal to 10.0 g/dl (transfusion within last 4 weeks), absolute neutrophil count greater than or equal to 1.5 x 10^9/L, platelets greater than or equal to 100 x 10^9/L
4.2. Total bilirubin less than 1.5 x upper normal limit

4.3. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than or equal to 2.5 x upper normal limit (or less than or equal to 5 x UNL in the presence of liver metastases)
4.4. Creatinine less than or equal to 1.5 x upper normal limit
5. Aged greater than or equal to 16 years, either sex
6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
7. Patients must have recovered from effects of major surgery
8. In view of concerns of possible teratogenicity, female patients must have no reproductive potential, i.e. must have a negative urine or serum pregnancy test within 7 days prior to start of trial, and must be post-menopausal
9. Males with reproductive potential should be prepared to use adequate contraception
10. Patient has provided written informed consent
11. Life expectancy of at least 12 weeks

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Added 01/03/2011: 122 (112 at time of registration)

Key exclusion criteria
1. Any chemotherapy, radiotherapy (except for palliative reasons), endocrine therapy or immunotherapy within four weeks prior to trial entry. Patients may continue the use of corticosteroids provided the dose is stable for 4 weeks and not altered during the first 15 days of the study.
2. Have received more than one course of chemotherapy for metastatic disease, and any previous treatment with ZD4054 or irinotecan. Where oxaliplatin has been used in an intermittent schedule allowing patient holidays it will be considered equivalent to one prior line of therapy providing that patients have at least stable disease whilst on active treatment.
3. Extensive prior irradiation (likely to deplete bone marrow reserve)
4. Major surgery within 4 weeks of starting the study
5. Co-existing active infection or serious concurrent medical condition
6. Significant cardiovascular disease as defined by:
6.1. History of congestive heart failure requiring therapy
6.2. History of unstable angina pectoris or myocardial infarction up to 6 months prior to trial entry
6.3. Presence of severe valvular heart disease
6.4. Presence of a ventricular arrhythmia requiring treatment
7. Any co-existing medical condition that in the investigators judgement will substantially increase the risk associated with the patients participation in the study or potentially hamper compliance with the study protocol and follow-up schedule
8. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or compliance with the study protocol
9. Bone metastases
10. Known brain or leptomeningeal metastases unless patients have stable disease following surgical resection or radiosurgery of oligometastases

11. Gastrointestinal disorders likely to interfere with absorption of the study drug (e.g., partial bowel obstruction or malabsorption)
12. Patients known to be serologically positive for hepatitis B or hepatitis C (mandatory testing not required)
13. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV) (mandatory testing not required)
14. Other previous or current malignant disease likely to interfere with protocol treatment or comparisons

Date of first enrolment
01/09/2009

Date of final enrolment
07/04/2012

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Leicester
Leicester
United Kingdom
LE15WW

Sponsor information

Organisation
Cardiff University (UK)

Sponsor details
Research and Commercial Division (RACD)
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30-36 Newport Road
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CF24 ODE

Sponsor type
University/education

Website

http://www.cf.ac.uk/racdv/index.html

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Charity

Funder Name
Astra Zeneca (UK) - providing ZD4054 and its distribution costs free-of-charge as an educational grant (subject to contract)

Funder Name
Cancer Research UK (CRUK) (UK) - WCTU is core funded by CRUK and WCTU core resources will be used to support this trial

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

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	results	01/02/2013		Yes	No
HRA research summary			28/06/2023	No	No