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A two-arm phase II randomised trial of intermittent chemotherapy plus continuous cetuximab and of intermittent chemotherapy plus intermittent cetuximab in first line treatment of patients with K-ras-normal (wild-type) metastatic colorectal cancer

Submission date 25/10/2006	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 04/01/2007	**Overall study status** Completed	
Last Edited 04/04/2022	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-chemotherapy-and-cetuximab-for-advanced-bowel-cancer

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2006-003049-17

IRAS number

ClinicalTrials.gov number
NCT00640081

Secondary identifying numbers
CR11

Study information

Scientific Title
A two-arm phase II randomised trial of intermittent chemotherapy plus continuous cetuximab and of intermittent chemotherapy plus intermittent cetuximab in first line treatment of patients with K-ras-normal (wild-type) metastatic colorectal cancer

Acronym
COIN-B

Study objectives
The primary questions in the COIN-B trial are about how biological therapy with cetuximab might be best added to chemotherapy, and about the benefits of intermittent chemotherapy.

On 17/02/2009 this record was extensively updated. All updates can be found under the relevant fields with the above update date. At this time, the title of this trial was updated. The initial title at the time of registration was: 'A two-arm phase II randomised trial of intermittent chemotherapy plus continuous cetuximab and of intermittent chemotherapy plus intermittent cetuximab in first line treatment of metastatic colorectal cancer'. Please also note that the target number of participants was changed from 136 to 158 and the overall trial end date was changed from 31/12/2008 to 31/12/2009.

On 07/02/2012 the following changes were made to the trial record:
1. The target number of participants was changed from 158 to 169.
2. The overall trial end date was changed from 31/12/2009 to 01/06/2010.

Ethics approval required
Old ethics approval format

Ethics approval(s)
South West Multi-Centre Research Ethics Committee, 18/12/2006, CTA: 00316/0220/001-0001

Study design
Interventional two-arm phase II randomised 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 request a patient information sheet

Health condition(s) or problem(s) studied
Metastatic colorectal cancer

Interventions
Amended as of 17/02/2009:
Patients with metastatic colorectal cancer (mCRC) who are fit for combination chemotherapy with the same inclusion criteria as the main COIN study and whose tumour is found to be K-raswt, will be randomised to receive either:

Arm D: intermittent chemotherapy plus intermittent cetuximab treatment comprising 12 weeks of chemotherapy plus cetuximab followed by a period off all therapy, with reintroduction of the same chemotherapy and cetuximab regimen for a further 12 weeks after initial progression off treatment

OR

Arm E: intermittent chemotherapy plus continuous cetuximab treatment comprising 12 weeks of chemotherapy plus cetuximab followed by a period of withdrawal of the chemotherapy, but continued weekly cetuximab monotherapy (maintenance cetuximab), with reintroduction of the same chemotherapy regimen to the cetuximab for a further 12 weeks after initial progression off chemotherapy treatment

Initial information at time of registration:
Patients with metastatic colorectal cancer who are fit for combination chemotherapy with the same inclusion criteria as the main COIN study, will be randomised at the start of chemotherapy to receive either:

Arm D: intermittent chemotherapy plus intermittent cetuximab treatment comprising 12 weeks of chemotherapy plus cetuximab followed by a period off all therapy, with reintroduction of the same chemotherapy and cetuximab regimen for a further 12 weeks after initial progression off treatment.

OR

Arm E: intermittent chemotherapy plus continuous cetuximab treatment comprising 12 weeks of chemotherapy plus cetuximab followed by a period of withdrawal of the chemotherapy, but continued weekly cetuximab monotherapy (maintenance cetuximab), with reintroduction of the same chemotherapy regimen to the cetuximab for a further 12 weeks after initial progression off chemotherapy treatment.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Cetuximab

Primary outcome measure
Failure-free survival at ten months.

Secondary outcome measures
Amended as of 17/02/2009:
1. To assess the safety of cetuximab reintroduction with regards to frequency of Grade 3 and 4 allergic reactions
2. To evaluate whether either arm will result in improved disease control (CR+PR+SD) at 24 weeks, overall survival, progression-free survival, response rates at 12, 24 and 36 weeks and toxicity
3. Quality of life

Initial information at time of registration:
1. To assess the safety of cetuximab reintroduction with regards to frequency of grade three and four allergic reactions
2. To evaluate whether either arm will result in improved disease control (CR+PR+SD) at 24 weeks, overall survival, progression-free survival, response rates at 12, 24 and 36 weeks and toxicity, and compare these outcomes in an indirect comparison with the main COIN arms

Overall study start date
01/12/2006

Completion date
01/06/2010

Eligibility

Key inclusion criteria
Amended as of 17/02/2009:
1. Written informed consent
2. Consent for screening of an archival formalin-fixed paraffin embedded (FFPE) tumour block for determination of K-ras status, with only patients with only K-raswt tumours being eligible for randomisation
3. Once K-raswt status confirmed, written informed consent for participation in the trial
4. Patients at least 18 years or over, either sex
5. Confirmed colorectal adenocarcinoma:
5.1. Either previous or current histologically-confirmed primary adenocarcinoma of colon or rectum, together with clinical or radiological evidence of current advanced and/or metastatic disease, or
5.2. Histologically/cytologically-confirmed metastatic adenocarcinoma, together with clinical and /or radiological evidence of colorectal primary tumour

6. Inoperable metastatic or locoregional disease
7. Patients with potentially resectable liver metastases are eligible (see exclusion criteria)
8. Unidimensionally measurable disease (Response Evaluation Criteria in Solid Tumours [RECIST] criteria). Baseline computed tomography (CT) scan must be performed within 4 weeks prior to treatment
9. No previous systemic palliative chemotherapy for metastatic disease
10. Adjuvant chemotherapy with 5FU +/- FA, capecitabine or irinotecan may have been given, if completed greater than 1 month prior to trial entry
11. Chemoradiotherapy with 5FU +/- FA or capecitabine for rectal cancer may have been given, if completed greater than 1 month prior to trial entry
12. World Health Organization (WHO) performance status (PS) 0, 1 or 2 and considered by responsible consultant to be fit to undergo combination chemotherapy
13. Baseline laboratory tests (within 1 week prior to randomisation):
13.1. Neutrophils greater than or equal to 1.5 x 10^9/l and platelet count greater than or equal to 100 x 10^9/l
13.2. Serum bilirubin less than or equal to 1.25 x upper limit of normal (ULN), alkaline phosphatase less than or equal to 5 x ULN, and serum transaminase (either aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) less than or equal to 2.5 x ULN
13.3. Estimated creatinine clearance (Cockcroft and Gault) greater than or equal to 50 ml/min or measured glomerular filtration rate (GFR) (ethylenediaminetetraacetic acid [EDTA] clearance) greater than or equal to 50 ml/min
14. For women of childbearing potential, negative pregnancy test and adequate contraceptive precautions
15. Effective contraception for male patients if the risk of conception exists
16. Written informed consent to allow pathological material to be analysed for estimated glomerular filtration rate (EGFR) status, even if this is already known

Initial information at time of registration:
1. Patients at least 18 years or over
2. Confirmed colorectal adenocarcinoma:
2.1. Previous or current histologically-confirmed primary adenocarcinoma of colon or rectum, together with clinical or radiological evidence of current advanced and/or metastatic disease
2.2. Histologically/cytologically-confirmed metastatic adenocarcinoma, together with clinical and /or radiological evidence of colorectal primary tumour
3. Inoperable metastatic or locoregional disease
4. Patients with potentially resectable liver metastases are eligible (see exclusion criteria)
5. Uni-dimensionally measurable disease (Response Evaluation Criteria in Solid Tumours [RECIST] criteria). Baseline computed tomography (CT) scan must be performed within four weeks prior to treatment
6. No previous systemic palliative chemotherapy for metastatic disease
7. Adjuvant chemotherapy with 5-fluorouracil (5FU) with or without folinic acid (FA), capecitabine or irinotecan may have been given, if completed more than one month prior to trial entry
8. Chemoradiotherapy with 5FU with or without FA or capecitabine for rectal cancer may have been given, if completed more than one month prior to trial entry
9. World Health Organization (WHO) performance status zero, one or two and considered by responsible consultant to be fit to undergo combination chemotherapy
10. Baseline laboratory tests (within one week prior to randomisation):
10.1. Neutrophils more than or equal to 1.5 x10^9/l and platelet count more than or equal to 100 x10^9/l
10.2. Serum bilirubin less than or equal to 1.25 x upper limit of normal (ULN), alkaline phosphatase less than or equal to 5 x ULN, and serum transaminases (either aspartate

transaminase [AST] or alanine transaminase [ALT]) less than 3 x ULN
11. Estimated creatinine clearance (Cockcroft and Gault Formula) more than or equal to 50 ml /min or measured glomerular filtration rate (GFR) (ethylenediaminetetraacetic acid [EDTA] clearance) more than or equal to 50 ml/min
12. For women of childbearing potential, negative pregnancy test and adequate contraceptive precautions
13. Effective contraception for male patients if the risk of conception exists
14. Written informed consent for participation in the trial
15. Written informed consent to allow pathological material to be analysed for estimated GFR (EGFR) testing

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
169 wild type patients

Total final enrolment
130

Key exclusion criteria
Amended as of 17/02/2009:
1. Patients who have a confirmed K-ras mutation in their tumour post screening
2. Patients who are receiving combination chemotherapy prior to the planned resection of operable liver metastases (defined as less than 4 unilobar liver metastases, each less than 4 cm in size and without major vascular involvement). Patients outside these criteria are of uncertain operability and are eligible.
3. Patients who have received any prior chemotherapy with oxaliplatin
4. Patients who are unfit for the chemotherapy regimens in this protocol, e.g.:
4.1. Severe uncontrolled concurrent medical illness (including poorly controlled angina or very recent myocardial infarction [MI], i.e. in previous 12 weeks) likely to interfere with protocol treatments
4.2. Any psychiatric or neurological condition which is felt likely to compromise the patient's ability to give informed consent or to comply with oral medication
4.3. Partial or complete bowel obstruction
4.4. Pre-existing neuropathy (greater than Grade 1)
5. Patients requiring ongoing treatment with a contraindicated concomitant
6. Patients with another previous or current malignant disease which, in the judgement of the treating investigator, is likely to interfere with COIN-B treatment or assessment of response
7. Patients with known hypersensitivity reactions to any of the components of the study treatments
8. Patients with brain metastases

9. Patients with a personal or family history of dihydropyrimidine dehydrogenase (DPD) deficiency, or with proven DPD deficiency

Initial information at time of registration:
1. Patients who are receiving combination chemotherapy prior to the planned resection of operable liver metastases (defined as less than four unilobar liver metastases, each less than 4 cm in size and without major vascular involvement). Patients outside these criteria are of uncertain operability and are eligible
2. Patients who have received any prior chemotherapy with oxaliplatin
3. Patients who are unfit for the chemotherapy regimens in this protocol, e.g.:
3.1. Severe uncontrolled concurrent medical illness (including poorly controlled angina or very recent Myocardial Infarction (MI), i.e. in previous 12 weeks) likely to interfere with protocol treatments
3.2. Any psychiatric or neurological condition which is felt likely to compromise the patient's ability to give informed consent or to comply with oral medication
3.3. Partial or complete bowel obstruction
3.4. Pre-existing neuropathy (more than Grade one)
4. Patients requiring ongoing treatment with a contraindicated concomitant medication
5. Patients with another previous or current malignant disease, which, in the judgement of the treating investigator, is likely to interfere with COIN-B treatment or assessment of response
6. Patients with known hypersensitivity reactions to any of the components of the study treatments
7. Patients with brain metastases

Date of first enrolment
01/12/2006

Date of final enrolment
01/06/2010

Locations

Countries of recruitment
Cyprus

England

United Kingdom

Study participating centre
MRC CTU
London
United Kingdom
WC2B 6NH

Sponsor information

Organisation
Medical Research Council (MRC) (UK)

Sponsor details
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Sponsor type
Research council

Website
http://www.ctu.mrc.ac.uk

ROR
https://ror.org/03x94j517

Funder(s)

Funder type
Industry

Funder Name
Merck KGaA (Germany)

Funder Name
Baxter Healthcare (UK)

Funder Name
Wyeth (UK)

Results and Publications

Publication and dissemination plan

Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan
Not provided at time of registration

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	01/05/2014		Yes	No
Plain English results			04/04/2022	No	Yes