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FOCUS 3 - the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer

Submission date
28/05/2009

Recruitment status
No longer recruiting

Registration date
24/07/2009

Overall study status
Completed

Last Edited
26/10/2022

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/study-using-gene-mutations-enzyme-decide-best-treatment-advanced-bowel-cancer

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT00975897

Clinical Trials Information System (CTIS)
2008-008323-15

Protocol serial number
CR12; 85362

Study information

Scientific Title
A randomised controlled trial to determine the feasibility of molecular selection of therapy using KRAS, BRAF and topo-1 in patients with metastatic or locally advanced colorectal cancer

Acronym
FOCUS 3

Study objectives
Test the feasibility of molecular testing. The primary outcome measures are:
1. Of those patients randomised, in how many patients was the interval between registration and the provision of results to the investigator to allow randomisation less than or equal to 10 working days
2. Of those patients randomised, in how many patients was the interval between registration and the date of randomisation less than or equal to 10 working days

As of 09/02/2010 this record has been updated to include an additional molecular test, from KRAS and topo-1 to KRAS, BRAF and topo-1. All changes can be found under the relevant section with the above update date. Please note that the title of this trial has changed to include this extra molecular test.

At this time, the anticipated end date of this trial was also updated; the previous anticipated end date was 01/07/2010.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Wales Research Ethics Committee (REC) on 26/05/2009

Study design
Randomised controlled trial

Primary study design
Interventional

Study type(s)
Diagnostic

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

Interventions
Amendments as of 09/02/2010:
Please note that as of the above date, the first line of the interventions has been edited as follows:

The first trial intervention is the analysis of KRAS, BRAF mutation status and topo-1 expression from archival formalin-fixed paraffin-embedded (FFPE) tumour blocks.

Initial interventions at time of registration:
The first trial intervention is the analysis of K-ras mutation status and topo-1 expression from archival formalin-fixed paraffin-embedded (FFPE) tumour blocks. This will be performed centrally in reference laboratories in Cardiff and Leeds, subject to documented Quality Assurance procedures. The control chemotherapy regimen for all four biomarker defined subgroups is irinotecan plus infusional 5FU and folinic acid (IrMdG) as per the best arm of the MRC FOCUS trial (Regimen A). There are four research regimens:
1. 5FU alone (MdG) (Regimen B)
2. 5FU, irinotecan plus oxaliplatin (IrOxMdG) (Regimen C)
3. IrMdG + cetuximab (Regimen D)
4. IrMdG + bevacizumab (Regimen E)

Capecitabine will not be allowed except for cases of venous access failure and individual cases must be discussed with MRC CTU prior to commencement of capecitabine treatment. Patients will continue on trial treatment for at least 24 weeks or until disease progression on treatment. After 24 weeks of treatment, patients may have a break of up to 6 weeks before restarting trial treatment. Once treatment has stopped, patients remain in the trial for the purpose of follow-up.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)
1. Of those patients randomised, in how many patients was the interval between registration and the provision of results to the investigator to allow randomisation less than or equal to 10 working days
2. Of those patients randomised, in how many patients was the interval between registration and the date of randomisation less than or equal to 10 working days

Key secondary outcome(s))
Amendments as of 09/02/2010:
Please note that as of the above date, the following points have been amended as follows:
4. In all randomised patients, time from the provision of KRAS, BRAF and Topo-1 results to the investigator to allow randomisation to the date of randomisation
5. Reproducibility of KRAS, BRAF mutation and topo-1 results between laboratory centres and methodological problems identified
6. Distribution frequencies of topo-1 expression and KRAS and BRAF mutation analysis and the distribution of patients between sub-groups to inform power calculations for the main study

Initial secondary outcome measures at time of registration:
1. Time from date of requesting hospital pathology laboratory to release a tumour sample to date of receipt of sample at central laboratory (Leeds or Cardiff)
2. Of those patients registered but not subsequently randomised, for what reasons did randomisation not occur (insufficient sample material, technical failure, unacceptable delay, patient refusal, patient ineligibility)

3. Time from registration consent to start of treatment
4. In all randomised patients, time from the provision of K-ras and Topo-1 results to the investigator to allow randomisation to the date of randomisation
5. Reproducibility of K-ras mutation and topo-1 results between laboratory centres and methodological problems identified
6. Distribution frequencies of topo-1 expression and K-ras mutation analysis and the distribution of patients between sub-groups to inform power calculations for the main study
7. Costs of the molecular testing
8. Toxicity, response rates and progression free survival (PFS) of the different regimens in the molecular subgroups
9. Attitude of patients to study design, the consent process and refusal rates for trial entry

Completion date
31/03/2011

Eligibility

Key inclusion criteria
Amendments as of 09/02/2010:
Please note that as of the above date, point 4 below was updated as follows:
4. Unidimensionally measurable disease (Response Evaluation Criteria in Solid Tumours [RECIST] criteria). Baseline computed tomography (CT) scan must be performed within 5 weeks prior to treatment.

Initial inclusion criteria at time of registration:
1. Male/female patients aged at least 18 years or over
2. Confirmed colorectal adenocarcinoma:
2.1. Either previous or current histologically confirmed primary adenocarcinoma of colon or rectum, together with clinical or radiological evidence of locally advanced disease or metastatic disease or both
2.2. Or histologically confirmed metastatic adenocarcinoma, together with clinical and/or radiological evidence of colorectal primary tumour
3. Inoperable metastatic or locoregional disease
4. 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.
5. Adjuvant chemotherapy with 5-fluorouracil (5FU) +/- folinic acid (FA), capecitabine or oxaliplatin combinations may have been given, if chemotherapy completed at least 6 months prior to trial entry. QUASAR 2 patients who have continued bevacizumab for 6 months following completion of chemotherapy are eligible immediately following completion of bevacizumab (Avastin).
6. Rectal chemoradiotherapy with 5FU +/- FA or capecitabine may have been given, if completed at least 1 month prior to trial entry
7. Fit to receive any of the treatment regimens proposed as defined by:
7.1. World Health Organization (WHO) performance status (PS) 0, 1 or 2 and considered by responsible consultant to be fit to undergo combination chemotherapy
7.2. Baseline laboratory tests (within 1 week prior to randomisation normally):
7.2.1. 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
7.2.2. Alkaline phosphatase less than or equal to 5 x upper limit of normal (ULN), serum bilirubin less than or equal to 1.25 x ULN and serum transaminase (either aspartate aminotransferase

[AST] or alanine aminotransferase [ALT]) less than or equal to 2.5 x ULN
7.2.3. Estimated creatinine clearance (Cockcroft and Gault) greater than or equal to 30 ml/min or measured glomerular filtration rate (GFR) (ethylenediaminetetraacetic acid [EDTA] clearance) greater than or equal to 30 ml/min
8. For women of childbearing potential, negative pregnancy test and adequate contraceptive precautions
9. Effective contraception for male patients if the risk of conception exists
10. Written informed consent including consent to the immediate release of tumour blocks for analysis of molecular markers

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Patients expected to be suitable for surgical resection of metastatic disease after response to chemotherapy as decided by the multidisciplinary team (MDT)
2. Previous systemic chemotherapy for metastatic disease
3. Pregnant or lactating women
4. Inability to attend or comply with treatment or follow-up scheduling
5. Patients who are unfit for the chemotherapy regimens in this protocol, e.g.:
5.1. Severe uncontrolled concurrent medical illness (including poorly controlled angina, uncontrolled hypertension or very recent myocardial infarction (MI) (i.e. in previous 3 months), likely to interfere with protocol treatments
5.2. History of severe peptic ulcer diseases
5.3. 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
5.4. Nephrotic syndrome
5.5. Known coagulopathy
5.6. Patients requiring ongoing therapy with ciclosporin-A (due to interaction with irinotecan)
6. Patients requiring ongoing treatment with a contraindicated concomitant medication
7. Patients with another previous or current malignant disease which, in the judgement of the treating investigator, is likely to interfere with FOCUS 3 treatment or assessment of response
8. Patients with known hypersensitivity reactions to any of the components of the study treatments
9. Patients with brain metastases
10. Patients with a personal or family history suggestive of dihydropyrimidine dehydrogenase (DPD) deficiency or with known DPD deficiency

11. History of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant precluding informed consent
12. History of surgery less than 4 weeks prior to commencement of cycle 1

Date of first enrolment
01/07/2009

Date of final enrolment
31/03/2011

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Velindre Hospital
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Sponsor information

Organisation
Medical Research Council (UK)

ROR
https://ror.org/03x94j517

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council (UK) (ref: 85362)

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

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	29/04/2014		Yes	No
Plain English results			26/10/2022	No	Yes