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Can extra tests on cancer samples identify more patients with bowel/colon cancer who should be treated with drugs called anti-EGFR agents?

Submission date 23/11/2021	**Recruitment status** Recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 30/11/2021	**Overall study status** Ongoing	
Last Edited 13/03/2025	**Condition category** Cancer	

Plain English summary of protocol

See also: https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-to-find-out-if-more-people-with-bowel-cancer-could-have-cetuximab-and-panitumumab-ariel

Background and study aims

Not all bowel (colon) cancers are the same. It is known that tumours which start in the right side of the bowel (right-sided), behave differently than those on the left side. Patients with advanced cancer (cancer that has spread to other areas) whose tumours are right-sided do not tend to live as long as those with left-sided. Right-sided tumours may not respond as well to drugs used to treat cancer. It is therefore important for researchers to find ways to improve the treatments and cancer outcomes for patients with right-sided tumours.

Anti-EGFR agents (cetuximab and panitumumab) are drugs that switch off the growth signals from the Epidermal Growth Factor Receptor (EGFR), which is a protein on the cancer cell which makes cancer grow and spread. We know that if a protein (RAS) is altered and becomes abnormal on the tumour then a patient will not respond to treatment with anti-EGFR drugs. Doctors now test the tumours of all patients and only treat those patients without these abnormal RAS proteins (RAS-wt) with anti-EGFR drugs.

These drugs are available to patients in the UK with RAS-wt advanced bowel cancer alongside chemotherapy. However, in some patients with RAS-wt cancers the drugs do not work, despite the proteins being normal. This means that patients experience unpleasant side effects without any benefits. Cancer researchers have tried to understand why some patients benefit from anti-EGFR drugs, and some do not.

Research has shown that some patients with tumours that start in the right side of the bowel do not respond to this treatment and in many countries anti-EGFR drugs are not recommended for patients with a right-sided tumour. UK data shows that some patients with right-sided bowel cancers respond well to anti-EGFR drugs, but some patients do worse and their cancer grows more quickly and the side effects are more severe, than when treated with chemotherapy alone. This creates a problem for oncologists and patients. An extra test to help identify patients with right-sided bowel cancer that are most likely to benefit from anti-EGFR drugs would help resolve this.

Further research has found different tumour proteins (EREG and AREG) that identify those

patients most likely to respond to anti-EGFR drugs, including patients with right-sided bowel cancers. Further research on the importance of this protein is needed before it can be used in clinics.

Who can participate?
Study participants will have been diagnosed with advanced bowel cancer which started on the right side of the abdomen (tummy). Participants will have a gene (RAS) which is normal i.e. RAS wild type (RAS-wt). Each participant is carefully assessed using tests to check that they are suitable for inclusion in the study. These include: blood tests, an assessment of medical history, clinical examination, a pregnancy test (where appropriate) and a CT scan.

What does the study involve?
Patients who are suitable will be randomised to receive treatment with chemotherapy alone or chemotherapy with anti-EGFR drugs. The chemotherapy given will be the standard treatment for this type of cancer. A computer will choose at random which participants receive an anti-EGFR agent, with the chemotherapy. Participants allocated to this treatment will discuss with their doctor which of the anti-EGFR agents, cetuximab and panitumumab, might be most suitable. The treatment is given every two weeks for as long as the drugs continue to control the cancer, and as long the treatment is tolerable.

What are the possible benefits and risks of participating?
We do not know for sure that the addition of an anti-EGFR drug will help control your cancer. Participants may therefore experience side effects from this drug without getting any benefit. Some patients with right-sided bowel cancer already receive treatment with an anti-EGFR agent as part of standard care. They do this in the hope that they may be one of the minority of patients where the drug does help control their cancer for a longer period of time.
If you are allocated to receive an anti-EGFR drug in this study, the drug may help control your cancer for a longer period of time than chemotherapy alone. Results from this trial may lead to a new test to help oncologists and patients make better decisions about their treatment. Further research on tumour samples may help us find new ways to treat patients with right-sided bowel cancers.

Where is the study run from?
St James's University Hospital (UK)

When is the study starting and how long is it expected to run for?
October 2020 to August 2026

Who is funding the study?
National Institute for Health Research (NIHR) (UK).

Who is the main contact?
Claire Dimbleby, ARIEL@leeds.ac.uk

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Study website
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Contact information

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Scientific

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Additional identifiers

EudraCT/CTIS number
2021-003330-36

IRAS number
298873

ClinicalTrials.gov number
Nil known

Secondary identifying numbers

CPMS 50663, NIHR129268, IRAS 298873

Study information

Scientific Title
A biomarker enrichment trial of anti-EGFR agents in patients with advanced colorectal cancer (aCRC) with wild-type RAS and right primary tumour location (right-PTL)

Acronym
ARIEL

Study objectives
Feasibility hypothesis: It is feasible to include EREG/AREG stratification in the clinical pathway for patients with aCRC?

Main hypothesis: patients with AREG/EREG-high, RAS-wt, rPTL aCRC have an improved cancer response measured by ETS rate if an anti-EGFR agent is added to first-line doublet chemotherapy.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/10/2021, Yorkshire & The Humber Leeds West Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 207 1048134; leedswest.rec@hra.nhs.uk), ref: 21/YH/0237

Study design
Interventional randomized 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 to request a patient information sheet

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

Interventions

Current interventions as of 30/04/2024:
Patients will be consented for registration and access to stored tumour material. RAS-wt or unknown RAS-status patients can be registered (central testing offered). After patient consent and registration, archival tissue will be retrieved and sent to a central laboratory for assessment of EREG/AREG ligand expression status (high vs low), and RAS status (if not assessed locally). EREG/AREG will be measured by reverse transcriptase polymerase chain reaction (RT-PCR) and dichotomised (either high vs both low) using predefined cut-points. The biomarker results will be fed back to sites via CTRU within 7-10 days.

Only EREG/AREG high patients will be eligible for randomisation. Eligible patients will be consented for randomisation and randomised to receive chemotherapy alone or chemotherapy plus anti-EGFR agent (cetuximab or panitumumab) on a 1:1 basis. Randomisation will be by minimisation with a random element, incorporating stratification for choice of first-line chemotherapy, tumour location, prior (neo)adjuvant chemotherapy and prior tumour resected.

Patients will be recruited from oncology clinics and treatment delivered in chemotherapy units. It is anticipated that 440 patients will need to be registered in order to randomise 162 EREG /AREG high participants. The recruitment period is 3 years. Participants will be followed-up for 1 year minimum for longer-term outcomes.

Patients whose tumours are EREG/AREG low will not be randomised, due to clear evidence of harm with anti-EGFR agents, but their baseline characteristics, treatment and outcome will be recorded.

Treatment and follow-up:
Treatment should start as soon as possible after randomisation. It is preferable that treatment begins following randomisation, but if a delay due to biomarker testing is unacceptable, then 1 cycle of chemotherapy is permitted prior to randomisation. Patients should be reviewed prior to each cycle of treatment to assess for toxicity and any evidence of disease progression (nurse-led and virtual pre-assessment is acceptable as per local practice).

The treatment schedules used are standard throughout the UK. Clinicians select either irinotecan- or oxaliplatin based regimes, based on the patient's preference (e.g. avoiding alopecia or peripheral neuropathy) and any prior adjuvant therapy. If allocated anti-EGFR therapy at randomisation, any licensed agent (cetuximab or panitumumab) may be used. Standard doses, schedules and adaptations for toxicity will be used. It is recommended that patients should have a DPYD germline mutation assessment to inform dosing of 5FU.

Patients will be assessed during and after treatment in line with standard good oncology practice. In order to ensure reliability of primary endpoint assessment (early tumour shrinkage at 8 weeks), a baseline CT scan of the thorax, abdomen and pelvis is mandated within 28 days prior to randomisation, or up to 7 days after randomisation. All patients will undergo a pre-treatment CT scan as part of routine care, however, it is anticipated that this may need to be repeated in up to 75% of (randomised) participants to ensure it is obtained within the trial-defined timeframe. A follow-up CT scan will be performed at 8 weeks and 16 weeks post-treatment start, which is in line with standard clinical care.

The study period is the first 16 weeks of 1st line chemotherapy. Mandating trial treatment beyond 16 weeks would not be acceptable to oncologists and patients. Following 16 weeks, treatment and radiological assessment will be at the discretion of the treating clinician. It is normal UK practice for patients with responding or stable disease to have a treatment break or reduced dose maintenance chemotherapy at this point.

Patients will complete health-related quality of life and health economics questionnaires pre-randomisation and at 8 weeks, 16 weeks and 12 months post start of treatment.

All patients will be followed-up in clinic to one-year post-randomisation as a minimum, with a final assessment in all patients when the last patient has completed a year of follow up – median 3.5 years follow up

Participating sites:
The study will recruit from up to 40 centres in the UK. This trial will be offered as an exemplar for the "Just-in-Time (JiT) site activation" pilot. JiT is a collaboration of NIHR CRN and Health Research Authority (HRA) for research with familiar therapies, but where smaller participating centres are anticipated to recruit ≤3 patients per year. A JiT trial undergoes a national assessment of the facilities, capabilities and experience needed to participate and is notified to all relevant Trust R&D teams, LCRNs and clinicians. Larger sites are set up prospectively as normal, but for smaller sites set-up is reactive, in response to an individual potential patient, with a 72-hour target from notification to approaching the patient. Full site set-up is triggered after 2 patients have entered using the JiT system. For this trial we anticipate 30 conventional and 10 JiT sites with the latter on a 'first-come, first-served' basis.

Biomarker testing:
Formalin-fixed paraffin embedded tumour blocks will be sent to Pathology & Data Analytics at the University of Leeds, an HTA-licensed laboratory with extensive experience of molecular testing in clinical trials. All material will be dealt with according to GCP, with processes overseen by a dedicated quality manager. If KRAS/NRAS/BRAF testing is required, sections will be cut for DNA extraction. Mutational analysis will be undertaken including KRAS codons 12/13/59/61/117 /146 and NRAS codons 12/13/59/61, and BRAF in keeping with UK recommendations.

Additional sections for RNA extraction plus H&E slide will be cut and sent to the University of Birmingham Surgical Research Laboratory (PI A Beggs), which will perform RNA extraction from the FFPE sections and determine EREG/AREG expression levels with standard housekeeping genes via RT-QPCR to GCP standards.

At the time of registration, consent will also be sought for the collection and storage of archival tissue for future research, and for ctDNA sampling at registration and (if randomised) on completion of the 16-week trial treatment period. Consent for future research and ctDNA sampling is optional and refusal will not preclude trial entry. If the patient has consented for their pathological material to be stored and used for future research, the tumour sample will be stored at the central laboratory in Leeds. Blood samples for ctDNA analysis will be stored in Birmingham. Note that tumour samples can be temporarily returned to site at any time during the study upon request to the CTRU, e.g. for further clinical testing.

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Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
irinotecan, oxaliplatin, cetuximab, panitumumab

Primary outcome measure
Early tumour shrinkage (ETS), measured 8 weeks after the start of treatment. This is taken as a binary variable with ETS defined as a 30% or greater reduction in the sum of maximum diameters (SMD) of RECIST target lesions when compared with the SMD recorded at baseline. SMD is measured from CT scans using calipers.

Secondary outcome measures
Current secondary outcome measures as of 30/04/2024:
1. Depth of response at 16 weeks from the start of treatment, measured as the maximum tumour shrinkage observed in a patient compared with baseline. This will be taken as a continuous measure.
2. Overall Treatment Utility (OTU), assessed at 8 weeks from the start of treatment. This is based on responses by clinician and participant regarding whether they were glad they gave or received their treatment allocation. OTU is scored as good, intermediate or poor, dependent on subjective measures of benefit or harm.
3. Overall survival (OS), measured from time of randomisation to death from any cause.

4. Patient-reported health-related quality of life (HRQOL), measured using the EORTC QLQ-C30 and EORTC QLQ-CR29 disease-specific module with additional items to cover anti-EGFR symptomatic toxicity using the EORTC-QLQ item library. This will be assessed at baseline, 8 weeks, 16 weeks and 12 months post-randomisation.
5. Cost-effectiveness, assessed by cost per incremental quality-adjusted life-year over a lifetime.
6. Toxicity, reported based on adverse events, as graded by CTCAE V5.0, and determined by routine clinical assessments at each centre

Previous secondary outcome measures:
1. Maximum tumour shrinkage measured using SMD up to 16 weeks.
2. Overall Treatment Utility (OTU), assessed at 8 weeks from the start of treatment. This is based on responses by clinician and participant regarding whether they were glad they gave or received their treatment allocation. OTU is scored as good, intermediate or poor, dependent on subjective measures of benefit or harm.
3. Overall survival (OS), measured from time of randomisation to death from any cause.
4. Patient-reported health-related quality of life (HRQOL), measured using the EORTC QLQ-C30 and EORTC QLQ-CR29 disease-specific module with additional items to cover anti-EGFR symptomatic toxicity using the EORTC-QLQ item library. This will be assessed at baseline, 8 weeks, 16 weeks and 12 months post-randomisation.
5. Cost-effectiveness, assessed by cost per incremental quality-adjusted life-year over a lifetime.
6. Toxicity, reported based on adverse events, as graded by CTCAE V5.0, and determined by routine clinical assessments at each centre

Overall study start date
21/10/2020

Completion date
31/08/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 30/04/2024:
Inclusion criteria for registration:
1. Age >=18 years
2. Biopsy-confirmed adenocarcinoma of the colon with a right primary tumour location (defined as proximal to and including the splenic flexure)
3. aCRC defined as either M1 or locally inoperable disease.
4. Tumour RAS status either wild-type (by local testing) or unknown
5. Tumour measurable by RECIST v1.1 criteria on CT scan (scans are not required to be reported to RECIST at site)
6. Pre-registration laboratory tests:
6.1. Neutrophils >=1.5 x10^9/l and platelet count >=100 x10^9/l
6.2. Serum bilirubin <=1.25 x upper limit of normal (ULN), alkaline phosphatase < = 5x ULN, and serum transaminase (either AST or ALT) <=2.5 x ULN
6.3. Estimated creatinine clearance >=50ml/min
7. Medically fit for the trial treatments
8. Sufficient tumour material for EREG/AREG analysis
9. Written informed consent for registration

Inclusion criteria for randomisation:
1. Registered in ARIEL
2. ARIEL central or local testing confirms tumour RAS-wt status
3. ARIEL central testing confirms tumour EREG/AREG high
4. Patients have had CT scan within the timeframes stipulated in the protocol. (If there is a contrast reaction, then non-contrast CT with MRI is acceptable assuming at least one of these modalities shows measurable disease at baseline for ETS evaluation and both modalities are repeated at the two trial timepoints at weeks 8 and 16.)
5. WHO performance status (PS) 0, 1 or 2
6. For women of childbearing potential, negative pregnancy test as per standard practice and adequate contraceptive precautions.
7. Effective contraception for male patients if the risk of conception exists.
8. Fit for combination chemotherapy plus cetuximab/panitumumab
9. Written informed consent for randomisation

Previous inclusion criteria:
Inclusion criteria for registration:
1. Age >=18 years
2. Biopsy-confirmed adenocarcinoma of the colon with a right primary tumour location
3. aCRC defined as either M1 or locally inoperable disease.
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7. Medically fit for the trial treatments
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2. ARIEL central or local testing confirms tumour RAS-wt status
3. ARIEL central testing confirms tumour EREG/AREG high
4. Patients have had CT scan within the timeframes stipulated in protocol
5. WHO performance status (PS) 0, 1 or 2
6. For women of childbearing potential, negative pregnancy test as per standard practice and adequate contraceptive precautions.
7. Effective contraception for male patients if the risk of conception exists.
8. Fit for combination chemotherapy plus cetuximab/panitumumab
9. Written informed consent for randomisation

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 440; UK Sample Size: 440

Key exclusion criteria
Exclusion criteria for registration:
1. Tumour RAS-mutation present
2. Prior chemotherapy for mCRC (may have received neoadjuvant or adjuvant chemotherapy provided disease did not progress on treatment, and > 6 months since last dose)
3. Prior anti-EGFR agent therapy

Exclusion criteria for randomisation:
1. Patient has received more than one cycle of chemotherapy since registration
2. Women who are breastfeeding
3. Patients with history of hypersensitivity to irinotecan, oxaliplatin, 5-fluorouracil or any of their excipients
4. Patients in receipt of live vaccine within four weeks prior to randomisation.
5. Patients with a history interstitial pneumonitis/idiopathic lung disease (ILD)
6. Patients with a history of keratitis, ulcerative keratitis or severe dry eye
7. Patients with a history of severe skin reaction which in the clinicians opinion could be exacerbated by EGFR Mab (cf Steven’s Johnson Syndrome)

Date of first enrolment
25/04/2022

Date of final enrolment
31/08/2025

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
St James's University Hospital
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Study participating centre
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Sponsor type
University/education

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Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC)

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/03/2027

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

Added 30/04/2024:
All relevant imaging (CT scans) should be made available for central review by the trial radiology team at Leeds Teaching Hospitals Trust. Key personal identifying data and the date of the CT scan/MRI scan will be required to identify and access the scans via the NHS imaging portal.

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IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No