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ARISTOTLE: a phase III trial comparing standard versus novel chemoradiation treatment (CRT) as pre-operative treatment for magnetic resonance imaging (MRI)-defined locally advanced rectal cancer

Submission date 28/10/2008	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 08/09/2009	**Overall study status** Completed	
Last Edited 03/10/2023	**Condition category** Cancer	

Plain English summary of protocol
http://cancerhelp.cancerresearchuk.org/trials/a-trial-looking-standard-treatment-with-without-irinotecan-cancer-rectum-aristotle

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2008-005782-59

Protocol serial number
Version 6.1

Study information

Scientific Title
ARISTOTLE: Advanced Rectal study wIth Standard Therapy Or a novel agent, Total mesorectal excision (TME) and Long term Evaluation

Acronym
ARISTOTLE

Study objectives
Some patients with rectal cancer benefit from receiving chemotherapy and radiotherapy before they have an operation to remove their cancers. This trial will determine whether the addition of a second drug (irinotecan) to the standard treatment of oral chemotherapy using capecitabine and radiotherapy will result in fewer cancer recurrences (regrowth) after the operation and if patients live longer.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee London - Riverside, 17/09/2010, ref. 10/H0706/65

Study design
Two-arm phase III multicentre randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Locally advanced rectal cancer

Interventions
Current interventions (as of 15/01/2018):
Arm A: capecitabine 900 mg/m^2 orally twice daily Monday to Friday for five weeks with radiotherapy 45 Gy in 25 fractions.
Arm B: irinotecan 60 mg/m^2 intravenously (IV) once weekly, weeks 1 - 4 and capecitabine 650 mg/m^2 orally twice daily Monday to Friday for five weeks with radiotherapy 45 Gy in 25 fractions.

All patients will be followed up for 5 years after completion of chemoradiotherapy.

Previous interventions
Arm A: capecitabine 900 mg/m^2 orally twice daily Monday to Friday for five weeks with radiotherapy 45 Gy in 25 fractions.

Arm B: irinotecan 60 mg/m^2 intravenously (IV) once weekly, weeks 1 - 4 and capecitabine 650 mg/m^2 orally twice daily Monday to Friday for five weeks with radiotherapy 45 Gy in 25 fractions.

All patients will be followed up for 5 years.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Irinotecan, capecitabine

Primary outcome(s)
Current primary outcome measures (as of 15/01/2018):
Disease free survival at 3 years after completion of chemoradiotherapy

Previous primary outcome measures as of 01/06/2016:
Disease free survival at 3 years

Previous primary outcome measures:
Disease free survival, assessed at four planned stages during the trial

Key secondary outcome(s))
Current secondary outcome measures (as of 15/01/2018):
1. Disease-specific survival
2. Loco-regional failure
3. Overall survival
4. Histopathologically confirmed circumferential resection margin (CRM) negative resection rate
5. Histopathological complete response pathological complete response (pCR) rate
6. Histopathologically quantitated tumour cell density
7. Surgical morbidity
8. Health-related Quality of Life (QoL) and functional outcome
9. Frequency and severity of adverse events
10. Compliance to trial treatment (radiotherapy, capecitabine and irinotecan)

Assessments weekly during treatment phase, then 1 and 4 weeks after completion of treatment, and then 4 - 6 weeks after completion of treatment.

Previous secondary outcome measures as of 01/06/2016:
1. Disease-specific survival
2. Loco-regional failure
3. Overall survival
4. Histopathologically confirmed circumferential resection margin (CRM) negative resection rate
5. Histopathological complete response pathological complete response (pCR)
6. Histopathologically quantitated tumour cell density
7. Surgical morbidity
8. Health-related Quality of Life (QoL) and functional outcome

Previous secondary outcome measures:
1. Disease-specific survival
2. Loco-regional failure
3. Overall survival
4. Histopathologically confirmed circumferential resection margin (CRM) negative resection rate
5. Histopathological complete response pathological complete response (pCR)
6. Surgical morbidity
7. Functional outcome
8. Quality of life
9. Resource use

Assessments weekly during treatment phase and then at 2 and 4 weeks after completion of treatment, and then 4 - 6 weeks after completion of treatment.

Completion date
29/12/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 01/06/2016:
1. Diagnosis of primary rectal cancer
2. Histologically confirmed invasive adenocarcinoma
3. Pelvic MRI defined disease (one of the following):
3.1. Mesorectal fascia involved or breached
3.1.1. Includes involvement of adjacent organ
3.2. Mesorectal fascia threatened (tumour ≤ 1 mm from mesorectal fascia) includes:
3.2.1. Primary tumour ≤ 1 mm from mesorectal fascia or
3.2.2. Extra-mural vascular invasion ≤ 1 mm from mesorectal fascia or
3.2.3. Tumour deposit with irregular border and mixed signal intensity ≤ 1 mm from mesorectal fascia
3.3. Low tumours at/below level of levators where:
3.3.1. Tumour ≤ 1 mm from levator on two imaging planes or
3.3.2. Tumour through full thickness of muscularis propria or beyond at level of puborectalis sling or below or
3.3.3. Tumour involving the intersphincteric plane or
3.3.4. Tumour involving the external anal sphincter
3.3.5. Patients with enlarged pelvic side wall nodes are eligible only if they also meet at least one of the above criteria.
4. Superior extent of macroscopic tumour no higher than S1/2 junction on saggital MRI
5. ECOG performance status 0 or 1
6. Considered fit to receive all trial treatments
7. Bowel function controlled with ≤ 6 mg loperamide per day
8. Absolute neutrophil count > 1.5 x 10^9/L; platelets > 100 x 10^9/L
9. Serum transaminase < 3 x ULN
10. Adequate renal function (Cockcroft-Gault estimation ≥ 50 mL/min)
11. Bilirubin < 1.5 x ULN
12. Able to swallow oral medication
13. Willing and able to give informed consent and comply with treatment and follow-up schedule
14. Aged 18 or over

Previous inclusion criteria:
1. Mesorectal fascia involved
2. Mesorectal fascia threatened (tumour less than 1 mm from mesorectal fascia)
3. Low tumours arising less than 5 cm from the anal verge
4. Patients aged 18 years and over, both male and female patients

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 01/06/2016:
1. Previous radiotherapy to the pelvis (including brachytherapy)
2. Uncontrolled cardiorespiratory comorbidity (includes patients with inadequately controlled angina or myocardial infarction within 6 months prior to randomisation)
3. Unequivocal evidence of metastatic disease (includes resectable metastases)
3.1. Patients with equivocal lesions (determined at MDT) are eligible
4. Major disturbance of bowel function (e.g. gross faecal incontinence or requiring > 6 mg loperamide each day)
5. History of another malignancy within the last 5 years except successfully treated non-melanoma cancer of skin or carcinoma in situ of uterine cervix
6. Known dihydropyrimidine dehydrogenase (DPYD) deficiency
7. Known Gilberts disease (hyperbilirubinaemia)
8. Taking warfarin that cannot be discontinued at least 7 days prior to starting treatment
9. Taking phenytoin or sorivudine or its chemically related anologues, such as brivudine
10. Gastrointestinal disorder which would interfere with oral therapy and its bioavailability
11. Pregnant, lactating, or pre menopausal women not using adequate contraception
12. Oral St John's Wort therapy that cannot be discontinued at least 14 days prior to starting treatment
13. Unfit to receive any study treatment or subsequent surgical resection

Previous exclusion criteria:
1. Patients unable or unfit to receive all study treatment
2. World Health Organization (WHO) performance status greater than or equal to 2
3. Metastatic disease
4. Pregnant or lactating

Date of first enrolment
25/10/2011

Date of final enrolment
29/06/2018

Locations

Countries of recruitment
United Kingdom

Study participating centre
103 centres
United Kingdom
-

Sponsor information

Organisation
Cancer Research UK and UCL Cancer Trials Centre (UK)

ROR
https://ror.org/054225q67

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (CRUK) (UK) (ref: C19942/A10016)

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Other publications	Modeling Acute Chemoradiotherapy (CRT) Diarrhea Severity Using Automatically Contoured Small Bowel	01/10/2023	03/10/2023	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes