1. SUMMARY OF TRIAL DESIGN

Title	A phase III trial comparing standard versus novel chemo-radiotherapy as pre-operative treatment for MRI defined locally advanced rectal cancer
Short Title	ARISTOTLE
EudraCT No.	2008-005782-59
Sponsor Name & No.	University College London – UCL /08/136
Funder Name & No.	Cancer Research UK – C19942/A10016
ISRCTN No.	ISRCTN09351447
Design	Randomised, multi-centre, phase III trial (two arm study)
Aim	To determine whether the addition of a second drug (irinotecan) to the standard treatment of oral chemotherapy using capecitabine and radiotherapy improves outcome
Primary Endpoint	• Disease-free survival (DFS)
Secondary Endpoints	• Disease-specific survival • Loco-regional failure • Overall survival • Histopathologically confirmed CRM negative resection rate • Histopathological complete response (pCR) rate • Histopathologically quantitated tumour cell density • Surgical morbidity • Health-related Quality of Life and functional outcome • Frequency and severity of adverse events • Compliance to trial treatment
Subjects	600 patients with MRI-defined locally advanced, non-metastatic rectal cancer
Inclusion Criteria	1. Diagnosis of primary rectal cancer 2. Histologically confirmed invasive adenocarcinoma 3. Pelvic MRI defined disease (one of the following): • Mesorectal fascia involved or breached • Mesorectal fascia threatened (tumour ≤ 1 mm from mesorectal fascia) • Low tumours at/below level of levators • 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 $\geq$ 1.5 x 10^9/L; platelets $\geq$ 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

Exclusion Criteria	1. Previous radiotherapy to the pelvis (including brachytherapy) 2. Uncontrolled cardiorespiratory comorbidity (including patients with inadequately controlled angina or myocardial infarction within 6 months prior to randomisation) 3. Unequivocal evidence of metastatic disease (includes resectable metastases) 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 (i.e. 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
No. of Sites	~100 centres
Target Countries	United Kingdom
Treatment Summary	Patients will be randomised to one of two pre-operative CRT regimens: • **Arm A** – Capecitabine 900 mg/m^2 orally twice daily, Mon-Fri for five weeks with radiotherapy 45 Gy in 25 fractions • **Arm B** – Irinotecan 60mg/m^2 once weekly (weeks 1-4); capecitabine 650 mg/m^2 orally twice daily, Mon-Fri for five weeks with radiotherapy 45 Gy in 25 fractions Surgery is strongly recommended to take place 8-10 weeks after completion of CRT. Post-operative adjuvant chemotherapy policy will be declared prior to randomisation and reflect local standard practice.
Anticipated Duration of Recruitment	6 years and 9 months
Duration of Patient Follow-up	Up to 5 years after completion of CRT
Definition of End of Trial	5.5 years after the last patient has been randomised, or once all patients have progressed or died, whichever happens first
Statistical Summary	The trial is powered to detect a 9% absolute improvement in 3 year DFS from 65% to 74%, which equates to a hazard ratio of 0.70, with power of 80% using a two-sided alpha of 0.05. This will require 247 DFS events which we expect to observe after recruiting 600 patients with a minimum of 3 years of follow-up.
Ancillary Studies	Blood samples and archival tumour tissue will be collected from consenting patients for future research.
Current Status	Open to recruitment
Chief Investigator	Professor David Sebag-Montefiore (St James Hospital, Leeds)
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2. TRIAL SCHEMA