NWCOG-2

'RICE'

A phase I/II study of Radiotherapy, Irinotecan, Capecitabine then Excision for locally advanced rectal cancer

North West/North Wales Colorectal Oncology Group (NWCOG)

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1 RATIONALE

1.1 Disease Background

There are approximately 35,000 new cases of colorectal cancer diagnosed per annum in the UK, with an annual death rate of approximately half of this (Cancer Research UK web site). Rectal cancer accounts for approximately 50% of these cases.

Both short course preoperative radiotherapy and the use of total mesorectal excision (TME) can lower the risk of local recurrence in operable rectal cancer (Heald and Karanija,'92; The Swedish Rectal Cancer Trial,'97; Kapitejin,'01). Prolonged course postoperative adjuvant chemoradiation can also lower the recurrence rate in rectal cancer at high risk of local recurrence (O'Connell, 94). Protracted infusion of 5-FU with postoperative radiotherapy improves survival versus bolus 5-FU (O'Connell,'94). Short course preoperative radiotherapy for all patients versus selective long course postoperative chemoradiation for patients at high risk of local recurrence, are currently being compared in the MRC CR07 trial.

Unfortunately, at least 20% of patients with rectal cancer present with locally advanced disease (T3/T4), correlating with partial or total fixation.Such patients are at increased risk of local recurrence and death (Duncan,'84) and in patients with involved resection margins, preoperative short course radiotherapy has been shown not to be of benefit (Kapitejin,'01).

1.2 Downstaging chemoradiation using 5-Fluorouracil as a radiosensitiser

It is known that if patients with locally advanced rectal cancer are treated with a prolonged course of radiotherapy, their tumours can be downstaged, resulting in higher resection rates (Emami,'82). The combination of chemotherapy and radiotherapy can apparently increase the efficacy of downstaging (Bosset,'93; Rich,'95).

5-Fluorouracil-based concurrent chemoradiation is becoming part of standard preoperative therapy for locally advanced rectal cancer, producing reported rates of pathological complete remission of 10-30%.

1.3 Capecitabine rather than 5-FU as a radiosensitiser

Capecitabine is a non-cytotoxic prodrug that is extensively absorbed from the gastrointestinal tract. It is converted via three metabolic steps to 5-FU. The first and second steps involve the liver but the third step (5'-DFUR to active 5-FU) occurs via the enzyme thymidine phosphorylase (TP). This enzyme is more active in tumour than normal tissue, resulting in a concentration of 5-FU in colorectal tumours that was 3.2 times higher than adjacent normal tissue in one study (Schuller,'00). Radiotherapy has been found to upregulate TP levels in a human cancer xenograft model, which further enhanced the efficacy of capecitabine (Sawada,'99). In this model, the antitumour

enhancement activity of capecitabine plus radiotherapy was considerably greater than that of 5FU plus radiotherapy.

Because of the above factors, there is a potentially enhanced therapeutic ratio from the use of capecitabine rather than 5FU concurrent with radiotherapy. In addition, there is the potential ease of administration of capecitabine when compared to continuous infusional 5-FU via a central venous catheter, resulting in potentially less inconvenience for patients.

In a German phase I study (Dunst,'02), radiotherapy to 45Gy in 25 daily fractions, with a presacral boost of 5.4Gy in 3 fractions, has been combined with continuous twice daily oral capecitabine throughout from days 1-37. Dose levels of 250, 375, 500, 650, 825 and 1,000 mg/m2 BD have been tested. The dose limiting toxicity (DLT) was found at 1,000 mg/m2 BD, when two of 6 patients developed G3 hand-foot syndrome. Twelve patients were treated at 825mg/m2 BD with no grade 3 or 4 toxicities occuring at this dose. At this dose level, there has been one pCR and nine PRs in 10 patients who received operations.

The NSABP R-04 trial is due to open in the USA in late 2003. The eligibility criteria for this trial include resectable, invasive rectal adenocarcinoma (T3-4, N0-2, M0), located less than 12 cm from the anal verge. Patients will be stratified by tumour stage (II vs III) and intended surgery (sphincter sparing vs other). All patients will receive radiotherapy to 45 Gy in 25 daily fractions over 5 weeks with a 5.4 Gy boost for non-fixed tumours or 10.8 Gy boost for fixed tumours. Patients will be randomly assigned to receive capecitabine 825 mg/m2 continuously during radiotherapy versus continuous infusion 5-FU at 225 mg/m2 during radiotherapy. There is a secondary randomisation in each arm of placebo versus rh-Erythropoeitin.

1.4 Irinotecan as a radiosensitiser in rectal cancer (+/-5FU)

Irinotecan is a topoisomerase-I inhibitor that has been licenced in the UK for the treatment of metastatic colorectal cancer in combination with 5-FU and folinic acid as first line and as monotherapy as second line treatment after failure of an established 5-FU containing treatment regime.

There is evidence that Topoisomerase-1 inhibitors can have radiosensitising properties (Eder,'97; Chen,'97). It is possible that the mechanism involves inhibition of DNA repair or in the inhibition of repair of potentially lethal radiation damage. The effect may be cell cycle specific (Falk,'92; Omura,'97).

Several early phase studies have now examined the combination of irinotecan with pelvic radiotherapy. In a phase I study, Minsky et al (1999) treated patients properatively with advanced rectal cancer using radiotherapy to 50.4 Gy in 5.5 weeks.

They received concurrent irinotecan Monday-Friday weeks 1,2,4 and 5 during radiotherapy. The MTD was declared to be 10 mg/m2, with one of 9 patients developing Gr3/4 diarrhoea and two needing radiotherapy delay at his dose level

In another phase I/II study (Mitchell et al,'03), 72 patients were treated with 45-54 Gy of radiation in 1.8 Gy daily fractions. They received a concurrent 5FU infusion throughout and a weekly 90 minute infusion of irinotecan on weeks 1, 2, 3 and 4. The MTD of irinotecan was found to be 50 mg/m^2 per week and that of 5FU, 225 mg/m^2. A pathological complete response (pCR) rate of 25% was found, with an additional 14% with microfoci of residual tumour.

Using a similar trial structure to Mitchell et al, Anne et al (2000) found that their MTD was 225 mg/m2/day of continuous infusional 5FU and 50 mg/m2 of irinotecan weeks 1,2,3 and 4. At this level two of nine patients exhibited grade 3 or 4 toxicity (not specified exactly which). Of 34 patients undergoing surgery in this study, 10 had a pCR and 6 microscopic residual disease.

Using the same radiotherapy regime, Falk et al (2002) have adopted a different approach, using a 1 hour infusion of 5FU at 350 mg/m2 plus bolus folinic acid at 20 mg/m2 on days 1-5 and 29-33 inclusive. Irinotecan at escalating doses is given via a one hour infusion before the 5FU and folinic acid on the same days. At a dose of 12 mg/m2 the MTD had not been reached.

1.5 Capecitabine and irinotecan combined as radiosensitisers in rectal cancer

Following on from the above considerations, there is a rationale to combining capecitabine and irinotecan together in an attempt to improve the efficiency of preoperative radiotherapy in locally advanced rectal cancer.

Kennedy et al (2002) delivered radiotherapy using 54 Gy as preoperative downstaging treatment in rectal cancers. Patients received weekly infusions of irinotecan at 50 mg/m2/week. In addition, they received capecitabine at 500 mg BD, 650 mg BD or 1,000 mg BD on radiotherapy days. The MTD had not been reached at a dose of 1,000 mg BD of capecitabine. All patients were staged uT3 or uT4 prior to chemoradiation. All were downstaged by at least one T-stage and there was one pCR.

2 STUDY OBJECTIVES

2.1 Primary objective

To determine the maximum tolerated dose (MTD) and the recommended dose of both intravenous irinotecan and capecitabine when given concurrently with a course of pelvic radiotherapy in patients who have locallly advanced rectal cancer. Radiotherapy is given to 45 Gy in 25 daily frations over 5 weeks. Capecitabine is given orally twice daily throughout their radiotherapy (including weekends). Irinotecan is given as a 60 minute intravenous infusion during weeks 1, 2, 3 and 4 of radiotherapy (with equal, weekly spacing between infusions).

2.2 Secondary objectives

To determine the toxicity profile of the combined regimen of capecitabine, irinotecan and pelvic radiotherapy by assessment of adverse events and abnormal laboratory values recorded during and up to 4 weeks after treatment.

To look for preliminary evidence of efficacy based on response rate and for those patients undergoing surgery, the resectability rate, histopathological complete response rate, T stage downstaging compared to the preoperative MRI scan.

To determine compliance with the planned dose of chemotherapy and radiotherapy.

To determine the late morbidity from the treatment regime by following patients for up to 3 years post surgery

3 STUDY DURATION

The study will start in September 2003. Recruitment is envisaged to continue until September-2004.

4 NUMBER OF CENTRES

Four in the UK: The North Wales Cancer Treatment Centre, Clatterbridge Centre for Oncology, Christie NHS Trust and Preston Centre for Oncology. Recruitment will be competitive. This number will be increased pending MREC approval.

5 SELECTION CRITERIA

5.1 Total number of patients

It is anticipated that approximately 50 patients will need to be recruited to complete the Phase II part of the study.

5.2 Inclusion criteria

1. Written informed consent given to participate in the trial.

2. Male or female patients aged ≥18 years old

3. WHO performance status 0,1 or 2 (Appendix 1).

4. Histologically confirmed previously-untreated carcinoma of the rectum with distal extent within 12 cm of the anal verge using a rigid sigmoidoscope.

5. Deemed to be a candidate for preoperative downstaging chemoradiation due to :

T3 disease on MRI scanning with disease ≤ 2 mm from the edge of the mesorectum

or T4 disease on MRI scanning

or any T3/T4 disease on MRI scanning with the distal extent of tumour ≤ 5 cm from the the anal margin.

6. Adequate haematology*: Neutrophil count>1.5 x 10^9/l, platelet count >100 x 10^9/l, Hb>9g/dl. The use of blood transfusions is allowed.

7. Adequate renal and hepatic function*: Serum creatinine ≤ 1.5x ULN, serum bilirubin ≤ 1.25 x ULN, serum ALT, AST and alkaline phosphatase ≤ 2.5 x ULN

* These assessments should be carried out within the 7-day period prior to study treatment.

5.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the trial.

1. Previous systemic chemotherapy

2. Previous radiotherapy to the planned exposure area.

3. Those unfit for resection because of metastases

4. Any severe concurrent medical condition which would make it undesirable, in the clinician's opinion, for the patient to participate in the trial or which would jeopardise compliance with the trial protocol.

5.Patients with a calculated creatinine clearance of less than 50 mls/min

6. Patients with loss of continuity of the upper GI tract or malabsorbtion

7. Patients who have suffered a myocardial infarction within last year and/or have unstable angina, arrythmia or cardiac failure

8. Pregnancy or lactation. Patients of child-bearing potential not implementing adequate contraception.

9. Previous or current malignancies at other sites, with the exception of adequately treated in-situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin.

10. Subjects considered by the investigator to be at risk of transmitting any infection through blood or other body fluid including Acquired Immune Deficiency Syndrome (AIDS), or other sexually transmitted disease or hepatitis.

11. Patient participation in other studies.

12. Partial or complete bowel obstruction. (Though patients in whom this has been relieved with a defunctioning stoma, are permitted to enter the trial).

5.4 Subject restrictions

The following restrictions should be applied to subjects in this trial:

1. Subjects who are blood donors should not donate blood during the trial and for 3 months following their last dose of trial treatment.

2. Subjects must not receive folic acid (including any vitamin supplements which contain folic acid).

3. Subjects must not receive any other concomitant systemic cancer therapy other than the trial treatment.

5.5 Pre-treatment investigations

Blood tests to be carried out within a week of study treatment:

Full blood count
Urea and electrolytes
Calculated creatinine clearance
Liver function tests
CEA

Radiology to be carried out within a month of trial registration:

Chest x-ray
Liver ultrasound or CT scan
Tumour biopsy
MRI pelvis

5.6 Registration procedure

Suitable patients will be recruited as they appear in clinics without regard to apportionment of patient numbers per centre, in order to complete the study in a timely manner. When a patient is screened in one centre and signs consent, the Department of Statistics at the Christie Hospital will be phoned on **0161 446 3311**, quoting **'NWCOG-2 Locally Advanced Rectal Cancer Study'**. The patient will then be assigned a dose group. A copy of CRF-1 should be forwarded to the Study Co-Ordinator. All Trials Centres will be kept regularly informed of patient numbers, toxicity and dose levels.

6 STUDY DESIGN

6.1 Design

An open-label dose escalating multicentre study.

6.2 Aim of study

To determine the maximum tolerated dose (MTD) and the recommended dose of both intravenous irinotecan and capecitabine when given concurrently with a course of pelvic radiotherapy in patients who have locallly advanced rectal cancer. Radiotherapy is given to 45 Gy in25 daily fractions over 5 weeks. Capecitabine is given orally twice daily throughout the radiotherapy (including weekends). Irinotecan is given as a 60 minute intravenous infusion during weeks 1, 2, 3 and 4 of radiotherapy (with equal, weekly spacing between infusions).

6.3 Structure of study

Patients will be assessed for eligibility prior to recruitment. From the point of view of acute toxicity, patients will be assessed weekly throughout their 5 week course of chemoradiation, then weekly for four weeks afterwards.

An MRI scan will be carried out at six weeks following radiotherapy completion then an attempt at surgery will take place eight weeks post radiotherapy completion.

From the point of view of late toxicity, patients will be assessed at 6, 12, 24 and 36 months post completion of radiotherapy.

6.4 Study medication

6.4.1 Capecitabine

Capecitabine is taken continuously throughout the 5 week course of radiotherapy. The capecitabine tablets are taken approximately 12 hours apart within 30 minutes of the ingestion of food (ideally after breakfast and evening meal) with approximately 200 ml of water (not fruit juices), and prior to radiotherapy on day 1. The starting dose of capecitabine (650 mg/m2) has been chosen taking into account the available early phase studies, paying regard to patient safety.

Capecitabine dose calculation according to body surface area

Capecitabine dose = 650 mg/m^2 bd		**Number of tablets to be taken at each dose (morning and evening)**	
Surface area (m^2)	**Twice daily dose (mg)**	**150 mg**	**500 mg**
< 1.46	900	6	-
1.47-1.66	1000	-	2
1.67-1.89	1150	1	2
1.90-2.12	1300	2	2
>2.13	1450	3	2

Capecitabine dose = 825 mg/m^2 bd		**Number of tablets to be taken at each dose (morning and evening)**	
Surface area (m^2)	**Twice daily dose (mg)**	**150 mg**	**500 mg**
< 1.48	1150	1	2
1.49-1.63	1300	2	2
1.64-1.76	1400	6	1
1.77-1.91	1500	-	3
1.92-2.09	1650	1	3
> 2.10	1800	2	3

6.4.2 Irinotecan

Irinotecan is given as a 60 minute intravenous infusion in 250 mls of normal saline during weeks 1, 2, 3 and 4 of radiotherapy (with equal, weekly spacing between infusions).

6.4.3 Overall study structure

The starting dose (dose level 1) of irinotecan is 50 mg/m2 and that of capecitabine is 650 mg/m2 bd. The doses are then gradually escallated as follows.

Dose Level	**Irinotecan (Weeks 1, 2, 3 + 4 of radiotherapy)**	**Capecitabine (daily throughout radiotherapy)**
-1	40mg/ m^2	650 mg/m^2 bd
1	50mg/ m^2	650 mg/m^2 bd
2	60mg/ m^2	650 mg/m^2 bd
3	60 mg/m^2	825 mg/m^2 bd
4	70 mg/m^2	825 mg/m^2 bd
5	80 mg/m^2	825 mg/m^2 bd

- There are 3 patients / cohort.
- If no grade 3 or 4 toxicity is encountered, further patients should be entered at the next dose level. Toxicity is assessed until four weeks post completion of radiotherapy i.e. nine weeks in total. The next dose level will not be available to recruitment until toxicity data is available for the whole nine week period for all patients on a particular dose level.
- If one patient develops grade 3/4 toxicity, then a further 3 patients will be added to this cohort.
- If there are no further episodes of grade 3/4 toxicity, then further patients should be entered at the next dose level.
- If at least 2 out of 6 patients at the same dose level develop grade 3 or 4 toxicity, then this is to be considered as dose limiting toxicity (DLT).
- The level below this is considered the maximum tolerated dose (MTD) and should be used for the remainder of the trial (phase II).
- The final cohort will be expanded to 50 pts to provide a confirmed recommended dose and to look at preliminary phase II evidence of response rate (Section 2.2).

6.5 Concomittant treatment

All concomittant medication should be reported on the case report form (CRF)

Subjects must not receive any other systemic anticancer therapy with the trial treatment. They should also not take vitamin supplements containing folic acid.

Dipyridamole (Persantin, Asasantin) should be avoided, as should Brivudin (Helpin)

There is interaction between capecitabine and coumarin-derivative anti-coagulants. Patients taking coumarin-derivative anti-coagulants require to have their anti-coagulation monitored closely and regularly when started on capecitabine and for at least a month after completing treatment.

Capecitabine should not be administered together with sorivudine (antiviral) or its chemically related analogues, such as brivudine. A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase (DPD) by sorivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.

Patients taking phenytoin concomittantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

7 RADIOTHERAPY

7.1 Treatment position

Prone, full bladder (depending on patient tolerance), anal marker, rectal contrast if orthoganol films are used for planning.
Opacification of the small bowel can be helpful (eg 300 ml Baritop plus 20 ml Gastrograffin orally 45-60 minutes prior to simulation).

7.2 Target volume

The Planned Target Volume (PTV) is defined using simulator planning or via Computerised Tomography planning.

The PTV is to include the following:

Lower third rectal tumours (lowest extent within 5 cm of anal verge)

Superior: 3 cm superior to most superior extent of the GTV
Inferior: 3 cm inferior to most inferior extent of the GTV
Posterior: Posterior border of the most posterior aspect of the sacrum
Anterior: 2 cm anterior to tumour or the anterior rectal wall whichever is the more anterior
Lateral: 3 cm lateral to the most lateral extent of GTV

Mid rectal tumours (lowest extent is >5 - 10 cm from anal verge)

Superior: 3 cm superior to the most superior extent of the GTV but PTV to extend no higher than the sacral promontory
Inferior: 3 cm inferior to the most inferior extent of GTV
Posterior: Posterior border of most posterior aspect of sacrum
Anterior: 2 cm anterior to tumour or the anterior rectal wall whichever is the more anterior
Lateral: 3 cm lateral to the most lateral extent of GTV

Upper third rectal tumours (lowest extent > 10-12 cm from anal verge)

Superior: 3 cm superior to the most superior extent of the GTV but PTV to extend no higher than the sacral promontory
Inferior: 3 cm inferior to the most inferior extent of GTV
Posterior: Posterior border of most posterior aspect of the sacrum
Anterior: 2 cm anterior to tumour or the anterior rectal wall whichever is the more anterior
Lateral: 3 cm lateral to the most lateral extent of GTV

7.3 Dose prescription

The prescribed dose will be at the central axis of the beams. In the central axis section, the dose within te target area should be no less than 95% and no more than 105% of the presribed dose. Off-axis dose should be recorded (1 cm inside the superior and inferior field borders). Treatment will be 45 Gy in 25 daily fractions, treating for 5 days per week, 1.8 Gy per day for five weeks. Three or four treatment fields are to be used and all fields are to be treated daily. Minor delays in the delivery of radiotherapy due to bank holidays or machine breakdown would not constitue a protocol violation.

7.4 Quality Assurance

Review of the Simulator films and plans will be made by a designated NWCOG member.

8 ACUTE TOXICITY AND DOSE ADJUSTMENT

Toxicity will be scored on a weekly basis during radiotherapy and then weekly for four weeks after completion of radiotherapy i.e. for a total of nine weeks, by telephone if necessary, according to CTC version 2.0 (published 30.4.99).

8.1 Dose modifications in the event of haematological toxicity (neutropaenia and thrombocytopaenia)

Toxicity grade CTC criteria	Radiotherapy	Capecitabine	Irinotecan
1	Continue	100%	100%
2	Continue	Interrupt until grade 0-1; then 100%	Interrupt until grade 0-1; then 100%
3 (without fever and not requiring supportive therapy)	Interrupt until grade 0-1	Interrupt until grade 0-1; then 75%	Interrupt until grade 0-1; then 75%
4 (or neutopenia G3/4 with fever requiring supportive therapy or thrombocytopenia G3 requiring supportive therapy)	Interrupt until grade 0-1	Discontinue treatment permanently (off study)	Discontinue treatment permanently (off study)

8.2 Dose modifications in the event of non-haematological toxicity (principally diarrhoea, stomatitis, mucositis)

Toxicity grade CTC criteria	Radiotherapy	Capecitabine	Irinotecan
1	Continue	100%	100%
2	Daily review	Interrupt until grade 0; then 100%	Interrupt until grade 0; then 100%
3	Daily review	Interrupt until grade 0; then 75%	Interrupt until grade 0; then 75%
4	Discontinue treatment unless symptoms settle to grade 0-1 within two weeks	Discontinue treatment	Discontinue treatment

If creatinine clearance falls below 30 ml/min during the study, then the patient should be withdrawn from the study because capecitabine is contraindicated in patients with severe renal impairment.

All standard supportive measures should be given to patients suffering side effects from treatment, including loperamide for diarrhoea, vitamin B6 (pyridoxin) for Hand-Foot Syndrome and appropriate treatment within existing local protocols for neutropenic sepsis.

In the event of severe toxicity, the. patient should receive full supportive care. It is recommended that patients with grade 3 or 4 diarrhoea should be admitted to hospital and treated with intravenous fluids, loperamide and antibiotics, especially when there is concomitant leucopenia. In the presence of rapidly falling serum albumin, total parenteral nutrition should be added. If leucopenia is protracted, in addition to folinic acid, G'CSF may be added, according to local practice.

8.3 Dose modifications of capecitabine in the event of Plantar-Palmar Erythrodysesthaesia (Hand-Foot Syndrome) if grade 2, 3 or 4 toxicity occurs

Toxicity grade CTC criteria	**1st appearance**	**2nd appearance**	**3rd appearance**	**4th appearance**
2	Interrupt treatment until resolved to grade 0-1, then continue at same dose with prophylaxis where possible	Interrupt treatment until resolved to grade 0-1, then continue at 75% of original dose	Interrupt treatment until resolved to grade 0-1, then continue at 50% of original dose	Discontinue treatment permanently (off study)
3	Interrupt treatment until resolved to grade 0-1, then continue at 75% dose with prophylaxis where possible	Discontinue treatment permanently (off study)	Discontinue treatment permanently (off study)	
4	Discontinue treatment unless investigator considers it in the best interests of the patient to continue at 50% of the original dose once toxicity has resolved to grade 0-1			

9 NWCOG-2 STUDY FLOW CHART

	Pre RT	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 11**	**Wk 13**	**pst op**	**6 m**	**12 m**	**24 m**	**36 m**

Physical exam	X													X	X	X	X
FBC	X	X	X	X	X	X	X	X	X	X							
U+E+creat	X	X	X	X	X	X	X	X	X	X							
Calc GFR	X		X	X	X	X											
LFT	X	X	X	X	X	X	X	X	X	X							
Histol confirm	X																
CEA	X										X						
Liver (US or CT)	X																
MRI pelvis	X										X						
CXR	X																
Consent form	X																
Surgery												X					
Baseline evaluation form (1)	X																
Treatment record form (2)		X	X	X	X	X											
Haem/Bioch toxicity form (3)	X	X	X	X	X	X	X	X	X	X							
Non-haem toxicity form (4)	X	X	X	X	X	X	X	X	X	X							
Post treatment summary (5)											X						
Surgeryl/histopathology form (6)													X				
Late toxicity form (7)														X	X	X	X

Serious Adverse Event Form (Appendix 2) as needed

Patient Withdrawal Form (CRF 8) as needed

10 ADVERSE EVENTS AND SUBJECT WITHDRAWALS

10.1 Definition of adverse events

An adverse event is defined as the development of a new medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product in a clinical trial. This definition includes events occurring during any run-in or wash-out periods, and any follow-up period specified in the trial protocol. The medical condition does not necessarily have a causal relationship with exposure to the medicinal product. A medical condition can be symptoms (such as nausea and chest pain), signs (such as a rash or enlarged liver) or abnormal results on investigation (including blood tests, X-rays, scans of various types or electrocardiogram).

For the purpose of this trial, any detrimental change in a subject's condition subsequent to them entering the trial and during the follow-up period-after the final treatment, should be considered to be an adverse event. When there is a deterioration in the condition for which the medicine is being used, there may be uncertainty as to whether this is lack of efficacy or an adverse event. In such cases, unless the reporting physician considers that the medicine contributed to the deterioration, or local regulations state to the contrary, the deterioration should be considered a lack of efficacy.

The development of a new cancer should be regarded as an adverse event. New cancers are those that are not the primary reason for the administration of the trial treatment and have been identified after inclusion into the clinical trial.

10.2 Recording of adverse events

All adverse events will be recorded on the CRFs provided. A description of the event, including its severity, duration, any action taken (e.g., treatment and follow-up tests) and the outcome, should be provided, along with the investigator's assessment of the relationship to the trial treatment. Where possible, undetermined causality should be clarified, with further investigations if necessary, so that definitive causality to treatment can be determined. For those adverse events which could be classified according to the NCIC-CTC recommendations for grading of acute and subacute toxic effects, the NCIC-CTC grade must also be recorded (see Appendix D), for all events, irrespective of whether the event is believed to be drug-related or not. All adverse events, including those that are ongoing at the end of any follow-up period, will be followed to resolution. Relevant clinical assessments and laboratory tests will be repeated, on at least a weekly basis, until final resolution or stabilisation of the event (s).

10.3 Serious adverse events

A serious adverse event is one that fulfils one or more of the following criteria:

- is fatal
- is life-threatening
- requires or prolongs hospitalisation .

- results in disability or incapacity
- is a congenital abnormality
- requires medical intervention to prevent permanent impairment or damage

Safety Reporting

UK and EU regulations require that pharmaceutical companies collect and report safety data to Regulatory Authorities if the company provides free drug, a dedicated grant, materials or diagnostic tests for a clinical study.

Therefore, Roche and Aventis will provide a dedicated grant for the above DDX study on the understanding that the following safety reporting requirements are complied with:

SAE reports must be completed and faxed to the Study Co-Ordinator **(Fax 01745 445258)** within 24 hours of the event occurring. All events will be followed until resolution (if applicable). Please ensure that you clearly state on the SAE form whether or not, in your opinion, the SAE has a reasonable suspected causal relationship to the Roche or Aventis product. The Study Co-Ordinator will report all SAEs, promptly to the MCA according to UK regulatory requirements.

In accordance with EU regulatory requirements SAE reports should also be faxed by the relevant Investigator, to the Roche UK Drug Surveillance Centre **(Fax: 01707 367582**; Telephone 01707 367587) and to the local Aventis office **(Fax: 01732 584081)**

A listing of all adverse events (serious and non-serious) which have occurred during the study will be provided to Roche and Aventis within six weeks of the end of the study by the Study Co-Ordinator. Roche and Aventis are required to include these adverse events in Periodic Safety Update reports which must be provided to the MCA.

10.4 Withdrawal of subjects

Subjects may be withdrawn , from the trial/schedule of assessments for any of the following reasons:

- protocol non-compliance (protocol deviation)
- withdrawal of informed consent
- deterioration in the subject's condition
- the subject being lost to follow-up
- the occurrence of a serious adverse event
- achievement of a specified endpoint
- cure or correction of the subject's condition

- no change in the subject's condition

The reason for withdrawal and the date of withdrawal from the trial must be documented on CRF 8.

Subjects must be followed for 28 days after the last treatment with Irinotecan, capecitabine or radiotherapy, which ever is the later, for new adverse events.

11 DATA AND STATISTICS

11.1 Data Management

Case report forms (CRFs) will be provided for the recording of all data. Data should be recorded directly and legibly onto the case report forms, preferably in black ball-point pen. If any data are not available, omissions will be indicated on the case report forms. Corrections should be made legibly and initialled and dated by approved personnel; the reasons for significant changes must be provided. Correction fluid or covering labels must not be used. Copies of the CRFs will be retained by the investigator. Original CRFs will be requested at the relevant times by the Study Co-Ordinator.

11.2 Pathological specimens

Patients will be asked to consent to the possible use of tumour specimens for future research for which further ethical approval will need to be obtained at that time.

11.3 Statistical considerations: Toxicity

Once the MTD has been found, for the chemoradiation regime, the recommended dose will then be expanded to 50 patients in order to study the safety and feasibility of this dose in a larger number of patients.

All patients who started their treatment will be included in the analysis of safety.

The laboratory data will be listed for each individual patient and values falling outside the normal range will be highlighted. Clinically relevant changes in laboratory parameters may be calculated, criteria for these will be defined. Appropriate summaries of the laboratory data will be made.

Adverse events will be reported for each individual patient and appropriate summaries, for example, by body system will be made. Separate summaries will be presented for adverse events and toxicities resulting from radiotherapy and chemotherapy.

11.4 Assessment of efficacy

All patients will be included in the analyses of efficacy.

Objective response, downstaging and resecability rates with 95% confidence intervals will be calculated.

12 ADMINISTRATIVE ASPECTS

12.1 Ownership

This study is the responsibility of the clinicians who have initiated it, and is partly supported by Aventis Pharma Limited and Roche Products Limited. Although these companies have requested that they be allowed to see and make comment on any proposed publications, ownership of the data and of any publications resides with the investigators.

12.2 Indemnity

The study is being conducted under the well recognised ethical framework of the Doctor & Dentist Exemption Scheme (DDX). Under the DDX scheme the responsibility for the management and well being of a patient is no different from everyday clinical practice, namely the attending physician and the hospital trust. Aventis Pharma and Roche Pharmaceuticals are, of course, liable on a no fault basis for the quality and fitness for use of their product.

13 ETHICAL CONSIDERATIONS

13.1 Declaration of Helsinki Agreement

The trial will be conducted in accordance with The Declaration of Helsinki (1964), as amended at Scotland (October 2000).

13.2 Ethics Committee

The investigator must submit this protocol, plus relevant consent forms and a subject information sheet, for independent review by a recognised Ethics Committee, and the protocol must be reviewed and approved by this Committee before the trial can start. The Ethics Committee should comprise medical professionals and non-medical members in accordance with local guidelines, and should meet ICH requirements. The committee should be experienced in reviewing trial protocols.

Subject recruitment will not start until satisfactory evidence of ethical approval is given to Roche and Aventis in writing. They will require written evidence that clearly identifies the trial, the protocol version, and the consent documents reviewed.

Amendments to the protocol will be submitted for ethical review before implementation.

14 REFERENCES

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Appendix 1

WHO INDEX FOR PERFORMANCE STATUS

Point	Description
0	Able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to do light work.
2	Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50 % of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix 2

SAE from an Investigator Led Clinical Trial

SAEs must be faxed within 24 hour to +44 (0)1732 584081 and +44(0)1707 367582

Please write clearly in BLACK ink and in BLOCK CAPITALS

Study No.						Randomisation date		Patient No.	Country UK
Patient Initials			Date of Birth			Age	Sex	Height (cm)	Weight (kg)
first	mid	last	day	Month	year		☐ male ☐ female		

Criteria for expedited reporting (tick all applicable)

Seriousness criteria:

- ☐ was life threatening
- ☐ required or prolonged inpatient hospitalization
- ☐ was persistently or significantly disabling/incapacitating
- ☐ is a congenital anomaly
- ☐ resulted in death
- ☐ is medically important

Did the patient take a **significant overdose?** ☐ No ☐ Yes

Date and type of report

Date of THIS report |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

Date reported to study staff |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

Report type: ☐ initial ☐ follow up

For follow-up report, give only changes to previous

Was this serious adverse event first reported as a non-serious adverse event? ☐ No ☐ Yes

IF YES, Date event

became serious |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

If event started BEFORE first dose of study medication

Did this event continue and worsen in intensity (severity and/or frequency) after the first dose of study medication? ☐ No ☐ Yes

Description of adverse event and duration

Diagnosis/syndrome of AE

_____

Component signs or symptoms (only if applicable) 1. _____ 2. _____
3. _____ 4. _____ 5. _____

Start of adverse event |__|__| |__|__| |__|__|__|__| (day) / (month) / (year) End of adverse event |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)

Duration if adverse event lasted less than 24 hours: |__|__|__| |__|__| |__|__| (hours) / (minutes) / (sec)

Time since last dose of study medication |__|__|__| |__|__| (hours) / (minutes)

Comments on adverse event:

_____

_____

This section continued on next page

Study No :	Patient No.

SAE from an Investigator Led Clinical Trial

Comments continued

Remedial measures

Study medication (select one)

- ☐ no change
- ☐ dosage increased due to event
- ☐ dosage decreased due to event
- ☐ discontinued and reintroduced, no event recurred
- ☐ discontinued and reintroduced, same event recurred
- ☐ discontinued and reintroduced, different event occurred
- ☐ discontinued due to event and subject withdrawn
- ☐ permanently discontinued for other reason
- ☐ other, *please specify* _____

Were there other countermeasures? ☐ No ☐ Yes

***If YES,* Medication** ☐ No ☐ Yes

Other *(please specify)* _____

Causal relationship

Is there a reasonable possibility that the adverse event is associated with the study medication?

☐ No ☐ Yes

*Whether **NO** or **YES**, an alternative explanation may be ticked and details given below:*

- ☐ underlying/concomitant illness
- ☐ possibly associated with concomitant drug(s)
- ☐ directly related to study procedures
- ☐ other known or suspected cause *(please comment)*

Intensity		Outcome		
	☐ mild ☐ moderate ☐ severe		☐ recovery without sequelae ☐ ongoing at time of report ☐ subject died	☐ recovery with sequelae ☐ event not resolved, follow-up not deemed necessary by investigator

Relevant medical history (e.g. previous diseases, surgery, allergies, pregnancy)

Study medication:

_____

(1) ☐ study medication (2) ☐ active comparator
(3) ☐ placebo (4) ☐ code not broken

Indication _____

Date started |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Date ended |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Daily dose _____ Unit _____ Route _____ Batch No. _____

Study No :	Patient No.

Study medication:

(1) ☐ study medication (2) ☐ active comparator
(3) ☐ placebo (4) ☐ code not broken

Indication _____

Date started |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Date ended |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Daily dose _____ Unit _____ Route _____ Batch No. _____

Concomitant medication

List those given at time of event – those given to treat adverse event should be listed under 'Comments' on page 1/2.

Drug	Daily dose	Unit	Route	Indication	Date started day / month / year	Date stopped day / month / year	Ongoing No Yes	*Causal relationship No Yes
[1]								
[2]								
[3]								
[4]								
[5]								
[6]								
[7]								

**Is there a reasonable possibility that the adverse event is associated with the concomitant medication?*

In case of death

Date of death
|__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Was an autopsy performed?
☐ No ☐ Yes ☐ planned
If YES, please provide a copy of the autopsy report

Was the death related to the study medication? ☐ No ☐ Direct consequence ☐ Indirect consequence

Cause of death *(tick all applicable)*

	No	Yes
Disease for which subject was enrolled into study	☐	☐
Other pre-existing condition(s)	☐	☐
Serious adverse event	☐	☐
Unknown	☐	☐

(*Further information will be requested)*

Cause(s) of death ranked in order of likelihood

1. _____
2. _____
3. _____
4. _____

Study No : **Patient No.**

SAE from an Investigator Led Clinical Trial

Investigator
Name and address:

Investigator
Date (day/month/year):

	Signature:

Appendix 3
Palmar-Plantar Erythrodysesthesia (Hand Foot Syndrome) toxicity grading

Toxicity grade	Clinical Domain	Functional Domain
1	Numbness, dysesthesia/parasthesia, tingling, painless swelling or erythema	Discomfort which does not disrupt normal activities
2	Painful erythema with swelling	Discomfort which affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

Appendix 4

PATIENT INFORMATION SHEET **NWCOG-2**

A phase I/II study of Radiotherapy, Irinotecan, Capecitabine then Excision for locally advanced rectal cancer (RICE)

You are being invited to take part in a research study (clinical trial). Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

This information sheet may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

Thank you for reading this

1. Why have I been chosen?

You have been diagnosed as having a cancer of the back passage (rectum). The growth is fairly bulky and shows a degree of attachment to the surrounding tissues. At present your surgeon feels that he would struggle to remove your tumour completely in an operation and that it would be advantageous if we could shrink your tumour down as best we can before attempting an operation. This will hopefully make it technically easier for your surgeon to remove your tumour.

2. What is the purpose of the study?

A well established way of attempting to shrink your type of tumour is by giving you a course of radiotherapy over a period of five weeks. An attempt at surgery is then made six to eight weeks after radiotherapy has been completed.

This is not successful in every case however, and it is thought that if you are given some drugs (chemotherapy) at the same time as having the radiotherapy, we can increase the success rate in shrinking your tumour. The drugs that we would like to investigate in this study are called capecitabine and irinotecan.

The first aim of the trial is to find out what are the doses of capecitabine and irinotecan that can safely be given to patients such as you, during radiotherapy.
Patients will initially be treated in a group of 3 at a dose of capecitabine and irinotecan which has been decided upon from the results of previous studies. If patients have no significant side-effects, then the next group of 3 patients will be entered on a dose slightly higher, and so on until we have reached a dose level that is likely to be tolerated by most patients. This is known as the “recommended dose”.
When the recommended dose has been found, all patients from then on will be given this dose, and the second aim of the trial will be to determine how effective this dose is in shrinking your type of tumour.
A total of 50 patients will be treated in this second part (phase) of the trial.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

4. What will happen to me if I take part?

The radiotherapy is given as a daily treatment, which usually takes approximately 10 minutes per day, using strong x-ray treatment to the tumour on your rectum. You will be treated once a day from Monday to Friday for five weeks, meaning that you will have 25 treatments in total.

The **capecitabine** is given as tablets twice a day by mouth, each day during your radiotherapy including weekends.

The **irinotecan** is given via an hour long drip into a vein in your arm, four times during your radiotherapy, in the 1st, 2nd, 3rd and 4th weeks of treatment.

We will be administering different doses of capecitabine and irinotecan to different patients to try and find out what are the maximum doses that we can safely give to patients in this situation. We will be keeping a close eye on side effects and recording these in detail which will involve weekly blood tests during your treatment and for 4 weeks afterwards.

Approximately six to eight weeks after your radiotherapy treatment has finished, you will have another scan to see how well your tumour has responded to the treatment. You will hopefully then have an operation to remove your tumour if this is deemed feasible.

5. Use of stored tissue for biological marker studies

We would like to ask permission from you to use the tissue samples that were collected from you at the time of initial biopsy of your rectal cancer and also the tissue that will be removed from you in the future, following chemoradiation, when hopefully you have the operation to remove your rectal cancer. We are not asking you to have any additional procedures or tests.

There are several factors (called biological markers) that researchers are interested in testing for, as they may help predict which rectal cancers will respond to treatment using chemoradiation and which will not. The aim would be that in the future, we could 'tailor' the treatment that patients receive, according to the characteristics of their individual tumour. We would like to carry out such tests on your tissue samples to look for such biological markers.

With all the new developments in medicine, our understanding of cancer will increase and it is likely that new tests will become available in the future. Because we do not know what will be discovered in the future and what additional tests may be appropriate, we are asking that you give permission for such studies now so that researchers would not need to contact you in the future as each new test is

developed. It is unlikely that what is learnt from these studies will have a direct benefit for you, but it could benefit patients like you in the future.

It is possible that the tests will involve some form of analysis of the genetic material in your tissue (i.e. DNA and RNA). However, the tests carried out will not be with the intention of looking at the risks or inherited tendencies of you or your other family members developing cancer or other diseases in the future.
If further tests as indicated above, are to be carried out on your samples, then it would be necessary for small pieces of tissue to be sent from the original hospital storage facility, to a specialist laboratory where the tests would be carried out. Before this was carried out, this would have to be agreed by the Trial Steering Committee. Tests will only be carried out if they are felt to contribute to our knowledge of the disease. Samples would be stored at the specialist laboratory for as long as was deemed necessary for the intended tests to be carried out.

To make sure that your identity is kept secret, your tumour sample would be sent for these tests marked only with a patient number, not your name. There would thus be no possibility of tracing the sample and its results to you.

There would be no intention to feed back any of your individual results to you or anybody else. The results for the whole patient group in the trial, however, will hopefully eventually be published in a freely-available peer-reviewed medical journal. Results for the whole group would be published and no individual patients would be identifiable.

Sometimes researchers find that tissue samples can help to establish products that could be patented and licensed. If this occurs from your tissue sample you would not benefit financially.

You do not have to give permission for the future testing of your stored tissue specimens. If you choose not to, then you may still participate in the NWCOG-2 trial.

6. What do I have to do?

If you are pregnant you cannot take part in this study. It is very important that you must take adequate contraceptive precautions to avoid either yourself becoming pregnant during your participation in this study if you are a woman, or your partner becoming pregnant during your participation in this study if you are a man. Any woman who finds that she has become pregnant while taking part in the study, or any man whose partner becomes pregnant while he is taking part in the study, should immediately tell their research doctor.

7. What are the alternatives for treatment?

The standard treatment, out of the trial, would be a 5 week course of radiotherapy delivered exactly as described in the present study, Monday to Friday treating once per day over five weeks to a total of twenty five treatments. At the same time, you would be given chemotherapy using a drug called 5-Fluorouracil. This is delivered via a portable pump connected to a small tube (or catheter), which is inserted into one of your large veins (via your elbow or chest wall). The pump would deliver the 5-

Fluorouracil 24 hours a day, 7 days per week during the five weeks of your radiotherapy. You would not have to stay in hospital.

8. What are the possible disadvantages and risks of taking part?

Side effects of radiotherapy

Radiotherapy combined with chemotherapy can irritate the bowel, causing a degree of diarrhoea that can get worse as treatment progresses. There may be a degree of skin redness and soreness in addition. There may be some irritation of the bladder, causing cystitis-type symptoms such as passing urine more frequently. Your doctor will be seeing you regularly throughout treatment and will give you the appropriate medicines and advice if these symptoms occur. These symptoms usually gradually subside in the month or so following the completion of radiotherapy.

Tiredness can be a side effect of treatment that can occasionally persist for a few weeks afterwards.

Side effects of chemotherapy

a) Early diarrhoea: Early diarrhoea can occur within 24 hours of receiving irinotecan. Symptoms such as sweating, stomach cramps or watery eyes may accompany this early diarrhoea, but we will automatically give you an injection in advance to stop this from happening meaning that it is very unlikely that you will get such symptoms. However, if they do occur, then tell the nurse in the chemotherapy unit. If the symptoms occur after you have got home from the hospital, during the first 24 hours after the irinotecan infusion, rest quietly and telephone the ward for advice.

b) Delayed diarrhoea: Occasionally more severe diarrhoea can occur at a later stage (after 24 hours) as a side effect of irinotecan chemotherapy and if left untreated this can be dangerous but it usually responds well to prompt treatment. If you develop diarrhoea that is accompanied by cramping in your abdomen or your bowels are open four or more times in 24 hours, or you find that you are consistently passing large quantities of liquid stools then:

Take two of the loperamide tablets provided, immediately, then another tablet every two hours.

Drink plenty of fluids for as long as the diarrhoea lasts.

You should also report your diarrhoea as soon as possible (preferably within 24 hours) to the radiographers, chemotherapy staff, or ward staff. If the diarrhoea does not settle, you may need a course of an antibiotic called ciprofloxacin, or if the diarrhoea is severe, or if you can't drink plenty or if you also have a temperature or feel unwell, you may need to be admitted to hospital for a period of observation.

A booklet which contains more information on how to manage diarrhoea will also be given to you.

Other side effects of chemotherapy

You may notice a change in taste for certain foods, or soreness in the mouth. Some patients find they feel sick, although actual vomiting is unusual. It is possible but

unlikely that you may develop a degree of dryness and soreness of your hands and feet which, if left untreated could blister and crack (called palmar-plantar erythema or hand-foot syndrome), and you may have some hayfever like symptoms such as a runny nose or sore, gritty eyes. All these side effects can usually be helped by medication. If severely affected, please talk to your oncology team. Under these circumstances it is usually possible to improve symptoms by reducing the dose of chemotherapy, without compromising the effectiveness of treatment.

Chemotherapy can also lower your blood count which means you can become anaemic, prone to infection, or prone to bleeding or bruising. Your blood count will be checked weekly, but you should also inform your doctor/nurse if you develop symptoms such as breathlessness (sometimes occurs with anaemia), or a temperature (over 37.5ºC) or other signs of infection (for example, sore throat, shivering, pain when passing urine)

It is also possible though unlikely, that your hair will thin during this treatment. If you find you are losing your hair, talk it through with your oncology nurse who will be able to support you. Hair loss is temporary and it will grow back when the chemotherapy stops.

Rare side effects of chemotherapy

Just occasionally we meet someone who is unusually sensitive to the effects of capecitabine chemotherapy, and the side effects described above occur more quickly and severely than for others. The reason for this is an unusual metabolism which means that the capecitabine stays in the bloodstream for longer after it has been given. If this happens, treatment is stopped until the problems have resolved, and it is usually possible to restart at a lower dose. This will not necessarily compromise effectiveness of treatment. Very rarely, chemotherapy can cause heart palpitations, chest pains, or poor coordination. It is most unlikely that you will be affected, but if you suspect you have one of these problems, please discuss it with your doctor.

If you become suddenly unwell between hospital visits, and especially if you develop a high temperature, shivering fits or severe diarrhoea, please seek advice immediately, either from your hospital team or your local GP.

9. What are the possible benefits of taking part?

It is not possible to state that you will benefit personally from this treatment and the chemotherapy drugs used in this study may not be any more effective than the 5-fluorouracil given as standard treatment. However, it may be possible that by having these drugs at the same time as having the radiotherapy we can increase the success rate of shrinking your tumour. The information obtained from this study may be useful in helping patients similar to yourself in the future.

10. What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your research doctor will make arrangements for your care to continue. If you decide to continue in the study, you will be asked to sign an updated consent form.

Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your care to continue

11. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements, in addition to those that would usually exist whenever you are treated within the NHS.

Aventis Pharma and Roche Products, as the manufacturers of the drugs you will be receiving, are of course liable on a no fault basis for the quality and fitness for use of their product.

If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

12. Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital such as informing the suppliers or regulatory authorities of any reactions to the drugs which will need to be monitored, will have your name and address removed so that you cannot be recognised from it. Your research doctor will be required to inform your GP if you decide to participate in the study.

The two drug companies supplying the drugs for the study will not have access to individual patient medical records or data. They will, however, in addition to information regarding drug reactions or side effects, be sent the overall study results once the data has been analysed. No individual patients will be named. The drug companies will be allowed to see the results before publication, but will not be permitted to make any changes to the results.

If you consent to take part in the research your medical records may be inspected by the authorised individuals from the hospital, the group organising the study, North West/North Wales Colorectal Oncology Group (NWCOG) or by regulatory authorities to check that the study is being carried out correctly, but you will not be contacted or receive any feedback in the future.

13. What will happen to the results of the research study?

At the end of the study, the results will be published in a peer-reviewed journal and/or presented at scientific meetings. You will not be identified in any publication about the study.

14. Who is organising the research?

This study is being organised by the North West / North Wales Colorectal Oncology Group, a group of Consultant Oncologists.

Aventis Pharma have agreed to supply Irinotecan at a reduced price for the purposes of the study, and together with Roche Products (who supply capecitabine), are

providing a study grant to help cover any additional costs to the hospitals where patients in the study are treated. The grant will also help to cover administrative costs. Your research doctor will not receive any personal payment if you take part in the study.

There are no traveling expenses available for patients taking part in the study.

15. What if I have any concerns?

If you have any concerns or other questions about this study or the way it has been carried out, you should contact the Investigator (*insert name and contact details), Research Nurse (insert name and contact details).*

If you wish to complain about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service Complaints Procedure will be available to you via the hospital complaints department (*insert name and contact details).*

Thank you for taking time to read this information sheet.

You will be given a copy of this Patient Information Sheet and the signed consent form to keep.

APPENDIX 5

CONSENT FORM NWCOG-2

A phase I/II study of Radiotherapy, Irinotecan, Capecitabine then Excision for locally advanced rectal cancer (RICE)

Name of Researcher:

Please initial box

Section 1 – Participation in this study

All data for the study will be coded to keep your identity confidential and you will not be contacted nor receive feedback on your personal results in the future.

1. I confirm that I have read and understand the information sheet dated .....…….. (version .....) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from NWCOG or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I understand that Aventis Pharma and Roche Products will have access to the results of the study, but not access to my medical notes and will not be able to identify me as an individual. ☐

5. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Section 2 – Optional consent for future biological marker studies on stored tissues

Please answer yes or no to the following statement:

	YES	NO
I give my permission for access to and testing of any stored pathological specimens for future biological marker studies (To make sure your identity is kept secret, your tumour sample will be sent to any specialist laboratories with your study patient number, not your name, and you will not be contacted in the future with regard to any results obtained. If you do not wish to give this permission you can still participate in the study)	☐	☐

Name of Patient	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 6
GP Letter NWCOG-2

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Dear Doctor

Your patient _____ has a locally advanced rectal cancer that needs an attempt at down staging before attempting surgery.

The standard practice for this is with a five week course of radiotherapy delivering 25 daily treatments.

We are interested in the question of whether treating patients concurrently during the radiotherapy, with chemotherapy, increases the effectiveness with which rectal cancers are downstaged. The current phase I / II trial uses oral Capecitabine (a 5-Fluorouracil prodrug) given twice a day throughout radiotherapy, together with a weekly one-hour intravenous infusion of Irinotecan during weeks 1, 2, 3 and 4 of radiotherapy. Cohorts of 3-6 patients are treated with gradually increasing doses of the two drugs. We will be monitoring side effects in these cohorts of patients closely, in order to determine the maximum tolerated dose (MTD).

In the phase II part of the trial, a total of 50 patients are being evaluated for effectiveness of this regimen using the recommended dose derived from the phase I part of the study.

Your patient has been fully warned of the potential side effects of chemotherapy and in particular the potential side effect of severe diarrhoea occurring more than 24 hours after receiving Irinotecan. The patient information sheet is enclosed with this letter.

Following completion of chemoradiation, there will then typically be an 8 week gap before an attempt at surgical resection, if this is deemed a viable proposition.

If you have any questions with regard to the above, do not hesitate to contact me.

Yours sincerely

Dr
Consultant Oncologist