Clinical trial results:
EXCITE: Erbitux, Xeloda, Campto, Irradiation Then Excision for locally advanced rectal cancer. (North West Clinical Oncology Group-04 on behalf of the NCRI rectal cancer subgroup)

Summary

EudraCT number	2007-006701-25
Trial protocol	GB
Global end of trial date	31 December 2016

Results information

Result version number	v1 (current)
This version publication date	07 January 2018
First version publication date	07 January 2018

Trial information

Trial identification

Sponsor protocol code	UCL/07/132

Additional study identifiers

ISRCTN number	ISRCTN86285819
ClinicalTrials.gov id (NCT number)	NCT00972881
WHO universal trial number (UTN)	-
Other trial identifiers	MHRA CTA No.: 20363/0228/001-0001

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	ctc.sponsor@ucl.ac.uk, University College London, ctc.sponsor@ucl.ac.uk
Scientific contact	ctc.sponsor@ucl.ac.uk, University College London, ctc.sponsor@ucl.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2012
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In a phase II setting in MRI-defined locally advanced rectal cancer to assess the downstaging effectiveness of preoperative chemoradiotherapy using capecitabine/ irinotecan/cetuximab plus radiotherapy using the primary endpoint of clear (R0) circumferential resection margin rate.

Protection of trial subjects:

UCL CTC provided safety information to the TMG on a periodic basis for review. Trial safety data was monitored to identify: • New adverse reactions to the trial treatment regimen or individual trial treatments; • A higher incidence in rare adverse events than is stated in the IB/SPC for a trial treatment; • Trial related events that are not considered related to the trial treatment regimen. Should UCL CTC have identified or suspected any issues concerning patient safety at any point throughout the trial, the CI or TMG would have been consulted for their opinion.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	United Kingdom: 70
Worldwide total number of subjects	82
EEA total number of subjects	82

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	52
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

82 patients were recruited in total, 70 within the United Kingdom and 12 in the Republic of Ireland. The trial was opened to recruitment on the 30/03/2009, the first patient was recruited on the 09/04/2009, the last patient was recruited on the 25/10/2011.

Pre-assignment

Screening details:

N/A

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Trial

Arm description:

Patients were treated with pelvic radiotherapy to a planned volume at a dose of 45 Gy in 25 daily fractions of 1.8 Gy treating 5 days per week from Monday-Friday for five weeks in total.
Concurrently they received oral capecitabine at 650 mg/m2 bd for 5 days per week on the days of radiotherapy only. In addition they received IV irinotecan at 60 mg/m2 once per week during the 1st, 2nd, 3rd and 4th weeks of radiotherapy. In addition, they received a loading dose of IV cetuximab at 400 mg/m2 one week before the commencement of radiotherapy then at 250 mg/m2 once per week during the 1st, 2nd, 3rd, 4th and 5th weeks of radiotherapy.
Six weeks post completion of chemoradiation (CRT) patients received an MRI scan to judge response. At eight weeks post CRT patients underwent surgery.

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	Xeloda
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral capecitabine at 650 mg/m2 bd for 5 days per week on the days of radiotherapy only.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	Irinotecan Hydrochloride, Campto
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV irinotecan at 60 mg/m2 once per week during the 1st, 2nd, 3rd and 4th weeks of radiotherapy.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	Erbitux
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

loading dose of iv cetuximab at 400 mg/m2 one week before the commencement of radiotherapy then at 250 mg/m2 once per week during weeks 1, 2, 3, 4 and 5 radiotherapy i.e. six doses of cetuximab in total

Number of subjects in period 1	Overall Trial
Started	82
Completed	80
Not completed	2
Physician decision	1
poor performance patient did not start treatment	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	82	82	
Age categorical			
Age at registration (years)			
Units: Subjects			
Adults (18-64 years)	52	52	
From 65-84 years	30	30	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	21	21	
Male	61	61	
WHO Performance Status			
Units: Subjects			
WHO PS 0	62	62	
WHO PS 1	20	20	
Defunctioning stoma			
Units: Subjects			
Ileostomy	3	3	
Colostomy	4	4	
None	75	75	
T-stage			
Units: Subjects			
T2	6	6	
T3	67	67	
T4	9	9	
N Stage			
Units: Subjects			
N0	14	14	
N1	42	42	
N2	26	26	
M-Stage			
Units: Subjects			
M0	82	82	
Mesorectal edge on MRI scan			
Units: Subjects			
Potentially involved (=<1mm gap)	43	43	
Involved, not breached	22	22	
Breached	17	17	
Distance of distal end of tumour from anal verge using rigid sigmoidoscopy (mm)			
n=63			

Units: mm median full range (min-max)	 50 0 to 130	 -	
Distance of distal end of tumour from anal verge using MRI (mm)			
n=78			
Units: mm median full range (min-max)	 50 0 to 120	 -	
Maximum superior-inferior tumour dimension (mm)			
n=76			
Units: mm median full range (min-max)	 51 5 to 110	 -	
Maximum tumour diameter in a plane perpendicular to the longitudinal central axis of the rectum (mm)			
Median (range) [n-55] Not measurable [n=25] Missing = [n=2]			
Units: mm median full range (min-max)	 28 10 to 100	 -	

End points

End points reporting groups

Reporting group title	Overall Trial

Reporting group description:

Patients were treated with pelvic radiotherapy to a planned volume at a dose of 45 Gy in 25 daily fractions of 1.8 Gy treating 5 days per week from Monday-Friday for five weeks in total.
Concurrently they received oral capecitabine at 650 mg/m2 bd for 5 days per week on the days of radiotherapy only. In addition they received IV irinotecan at 60 mg/m2 once per week during the 1st, 2nd, 3rd and 4th weeks of radiotherapy. In addition, they received a loading dose of IV cetuximab at 400 mg/m2 one week before the commencement of radiotherapy then at 250 mg/m2 once per week during the 1st, 2nd, 3rd, 4th and 5th weeks of radiotherapy.
Six weeks post completion of chemoradiation (CRT) patients received an MRI scan to judge response. At eight weeks post CRT patients underwent surgery.

Primary: Primary endpoint

End point title	Primary endpoint[1]

End point description:

Histologically confirmed R0 resection rate i.e. the carcinoma is resected with margins clear by >1mm

End point type	Primary

End point timeframe:

Resection was recommended 8 weeks after completion of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The page would not allow us to enter a single arm comparison group, the error stated two arms had to be selected, whereas the help said a single arm can be selected if it is a single arm trial. Excite is single arm and it would not accept this so we deleted the data to be able to submit and have emailed EudraCT for guidance.

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Number of R0 resections				
R0	67			
R1	8			
R2	1			
Did not have surgery	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Radiotherapy compliance

End point title	Radiotherapy compliance

End point description:

End point type	Secondary

End point timeframe:
Completion of radiotherapy

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Compliance rate				
Full dose (45 Gy) received without delay as per pr	47			
Full dose (45 Gy) received with delay due to adver	29			
Dose reduction	4			
Did not start	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Grade 3 toxicity

End point title	Grade 3 toxicity

End point description:

End point type	Secondary

End point timeframe:
Grade 3 adverse events occurring during and up to 4 weeks following completion of CRT (based on 81 patients that had some treatment)

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Grade 3 toxicity				
Anaemia	1			
Leucopoenia	5			
Thrombocytopenia	0			
Neutropenia	4			
Febrile neutropenia	1			
Any haematological AE	10			
Diarrhoea	20			
Acneiform rash	7			
Fatigue	6			
Dehydration	1			
Pyrexia/Fever	1			
Headache	1			
Insomnia	1			

Taste disturbance	1			
Nausea	1			
Vomiting	1			
Urticaria	1			
Other rash/skin reactions	7			
Anal/rectal/bowel complications	6			
Thrombotic event	1			
Other	4			
Any non-haematological adverse event	36			
Any adverse event	38			

Statistical analyses

No statistical analyses for this end point

Secondary: Grade 4 toxicity

End point title	Grade 4 toxicity

End point description:

End point type	Secondary

End point timeframe:

Grade 4 adverse events occurring during and up to 4 weeks following completion of CRT (based on 81 patients that had some treatment)

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Grade 4 adverse events				
Anaemia	1			
Leucopoenia	1			
Thrombocytopenia	1			
Neutropenia	1			
Febrile neutropenia	1			
Any haematological AE	4			
Diarrhoea	0			
Acneiform rash	0			
Fatigue	0			
Dehydration	0			
Pyrexia/Fever	0			
Headache	0			
Insomnia	0			
Taste disturbance	0			
Nausea	0			
Vomiting	0			
Urticaria	0			
Other rash/skin reactions	0			

Anal/rectal/bowel complications	0			
Thrombotic event	5			
Other	1			
Any non-haematological adverse event	6			
Any adverse event	10			

Statistical analyses

No statistical analyses for this end point

Secondary: pathological complete response

End point title	pathological complete response

End point description:

End point type	Secondary

End point timeframe:

36 months

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: tumour regression grade				
grade 0	10			
grade 1	11			
grade 2	18			
grade 3	17			
grade 4	6			
grade 5 cPR	14			
did not have surgery	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

Up to 36 months post registration

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: 36 months PFS				
number (confidence interval 95%)	67 (55 to 76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:
up to 36 months from registration

End point values	Overall Trial			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: 36 month OS				
number (confidence interval 95%)	80 (69 to 87)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

signing of informed consent and 36 months after patient completes CRT

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Single arm

Reporting group description:

Patients were treated with pelvic radiotherapy to a planned volume at a dose of 45 Gy in 25 daily fractions of 1.8 Gy treating 5 days per week from Monday-Friday for five weeks in total.
Concurrently they received oral capecitabine at 650 mg/m2 bd for 5 days per week on the days of radiotherapy only. In addition they received IV irinotecan at 60 mg/m2 once per week during the 1st, 2nd, 3rd and 4th weeks of radiotherapy. In addition, they received a loading dose of IV cetuximab at 400 mg/m2 one week before the commencement of radiotherapy then at 250 mg/m2 once per week during the 1st, 2nd, 3rd, 4th and 5th weeks of radiotherapy.
Six weeks post completion of chemoradiation (CRT) patients received an MRI scan to judge response. At eight weeks post CRT patients underwent surgery.

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 81 (28.40%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
vessel injury - artery			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
hypotension			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

vasovagal episode				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
pulmonary embolism				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
thrombosis/thrombus/embolism				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	4 / 81 (4.94%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
febrile neutropenia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Lethargy				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

pyrexia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
asthenia				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
diarrhoea				
subjects affected / exposed	10 / 81 (12.35%)			
occurrences causally related to treatment / all	10 / 10			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
bowel obstruction				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
vomitting				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 81 (2.47%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				

Salmonella			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
perianal abscess			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
respiratory infection			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
dehydration			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 81 (85.19%)		
Investigations			
alanine aminotransferase increased			
subjects affected / exposed	28 / 81 (34.57%)		
occurrences (all)	28		
alkaline phosphatase increased			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	7		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Blood bilirubin increased			

subjects affected / exposed	9 / 81 (11.11%)		
occurrences (all)	9		
creatinine increased			
subjects affected / exposed	10 / 81 (12.35%)		
occurrences (all)	10		
GGT increased			
subjects affected / exposed	17 / 81 (20.99%)		
occurrences (all)	17		
Neutrophil count decreased			
subjects affected / exposed	24 / 81 (29.63%)		
occurrences (all)	24		
other investigations			
subjects affected / exposed	22 / 81 (27.16%)		
occurrences (all)	22		
platelet count decreased			
subjects affected / exposed	13 / 81 (16.05%)		
occurrences (all)	13		
white blood cell decreased			
subjects affected / exposed	40 / 81 (49.38%)		
occurrences (all)	40		
Injury, poisoning and procedural complications			
dermatitis radiation			
subjects affected / exposed	11 / 81 (13.58%)		
occurrences (all)	11		
Other injury, poisoning and procedural complication			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Nervous system disorders			
dizziness			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Dysgeusia			

subjects affected / exposed	8 / 81 (9.88%)		
occurrences (all)	8		
lethargy			
subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	19		
Blood and lymphatic system disorders			
Anemia/Hemoglobin increased			
subjects affected / exposed	46 / 81 (56.79%)		
occurrences (all)	46		
General disorders and administration site conditions			
fatigue			
subjects affected / exposed	46 / 81 (56.79%)		
occurrences (all)	46		
Fever neonatal			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	28 / 81 (34.57%)		
occurrences (all)	28		
Anal pain			
subjects affected / exposed	8 / 81 (9.88%)		
occurrences (all)	8		
Anal/oral mucositis			
subjects affected / exposed	17 / 81 (20.99%)		
occurrences (all)	17		
Constipation			
subjects affected / exposed	30 / 81 (37.04%)		
occurrences (all)	30		
Diarrhoea			
subjects affected / exposed	59 / 81 (72.84%)		
occurrences (all)	59		
Dyspepsia			
subjects affected / exposed	10 / 81 (12.35%)		
occurrences (all)	10		
lower gastrointestinal hemorrhage			

subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	25 / 81 (30.86%)		
occurrences (all)	25		
Proctitis			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	7		
rectal pain			
subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	19		
vomiting			
subjects affected / exposed	13 / 81 (16.05%)		
occurrences (all)	13		
Skin and subcutaneous tissue disorders			
alopecia			
subjects affected / exposed	6 / 81 (7.41%)		
occurrences (all)	6		
Erythema multiforme			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
other skin and subcutaneous tissue disorders			
subjects affected / exposed	8 / 81 (9.88%)		
occurrences (all)	8		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	24 / 81 (29.63%)		
occurrences (all)	24		
rash acneiform			
subjects affected / exposed	69 / 81 (85.19%)		
occurrences (all)	69		
skin ulceration			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Psychiatric disorders			

insomnia			
subjects affected / exposed	15 / 81 (18.52%)		
occurrences (all)	15		
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
urinary frequency			
subjects affected / exposed	8 / 81 (9.88%)		
occurrences (all)	8		
Infections and infestations			
Anorectal infection			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	5		
other infections and infestations			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
anorexia			
subjects affected / exposed	14 / 81 (17.28%)		
occurrences (all)	14		
hypernatremia/hyponatremia			
subjects affected / exposed	17 / 81 (20.99%)		
occurrences (all)	17		
hypermanesemia/hypomagnesemia			
subjects affected / exposed	19 / 81 (23.46%)		
occurrences (all)	19		
hypoalbuminia			
subjects affected / exposed	22 / 81 (27.16%)		
occurrences (all)	22		
hypocalcemia/hypercalcemia			
subjects affected / exposed	13 / 81 (16.05%)		
occurrences (all)	13		
hypokalemia/hyperkalemia			
subjects affected / exposed	21 / 81 (25.93%)		
occurrences (all)	21		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2008	Trial documentation changed to advise not to take St John's Wort whilst receiving Irinotecan, exclusion criteria and patient information sheet changed.
28 July 2008	•Section 14 Pharmacovigilance- whole section has been replaced with current CTC PV template. Contains more detailed and specific information with regards to reporting procedures.
08 August 2008	Change in concentration of cetuximab increasing from 2mg/ml to 5mg/ml
16 October 2008	• Introduction- additional paragraph added regarding Kras testing • Statistical considerations- last paragraph amended to reflect the new additional paragraph regarding Kras • Pharmacovigilance- whole section deleted and new CTC template inserted to reflect current procedures • Ancillary studies- new paragraph added regarding Kras testing
24 February 2009	Amendment to protocol and PIL. MRI assessment changed from needing to be within 28 days of start of treatment to registration.
07 May 2010	• Increase in recruitment target by an additional 40 patients • Inclusion criteria updated and an increase in baseline investigations timelines • Extra information for quality control of radiotherapy & pathology clarification • Change to trial drug distribution • Monitoring and PV changes and minor administrative amendments
20 October 2010	Amendment to capecitabine label. Irinotecan now to be supplied from hospital stock and will not need a clinical trial specific label.
04 January 2012	• Updates to sections 14 (Trial monitoring and Oversight), 15 (Pharmacovigilance), 16 (Incident reporting and Serious Breaches), 17 (Ethics and Regulatory approvals) and 18 (Sponsorship and indemnity) of the protocol to reflect current internal procedures and practices. • Amendment to section 19 (Biological Studies); Addition of further biological Studies, which was previously omitted from the protocol & clarification regarding immunohistopathological investigations.
22 January 2015	Change of end of trial definition updated to the 31st August 2015 to allow for translational studies to be performed. Timeframe in which adverse events are collected has been amended to 36 months post CRT. Addition of appendix 4 – Translational Studies and Methodology.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

09 February 2010	Interruption to recruitment, 40 patients reached and sites temporarily closed to recruitment, re-opened in August 2010. Reactivation teleconferences held, re-initiation for sites who did not recruit prior to interruption.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28859058