Clinical trial results:
XERXES: Examining the role of early neoadjuvant and synchronous Erbitux in pre-operative chemo-radiotherapy using Xeloda followed by excisional surgery.
A phase I/II dose escalation study of intravenous erbitux (cetuximab) in combination with 5 day weekly oral Xeloda (capecitabine) and preoperative radiotherapy in rectal cancer.

Summary

EudraCT number	2004-001926-26
Trial protocol	GB
Global end of trial date	30 November 2015

Results information

Result version number	v1 (current)
This version publication date	11 December 2016
First version publication date	11 December 2016

Trial information

Trial identification

Sponsor protocol code	XERXES

Additional study identifiers

ISRCTN number	ISRCTN11319909
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	MHRA CTA No.: 20363/0205/001

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, CR UK & UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	ctc.sponsor@ucl.ac.uk, CR UK & UCL Cancer Trials Centre, 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	30 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2015
Global end of trial reached?	Yes
Global end of trial date	30 November 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and toxicity of the combination of erbitux, capecitabine and radiotherapy. This will be determined through an assessment of the patient’s toxicity

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	01 July 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	13
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

12 patients were entered into phase 1 of the trial receiving Cetuximab prior to chemoradiation (Cisplatin). 10 patient's were entered into phase 2, with 5 patient's randomised to Arm A (Capecitabine and radiotherapy) and 5 randomised to Arm B (Cetuximab, capecitabine and radiotherapy). Recruitment spanned 01/07/05 - 01/10/12 at UK sites.

Pre-assignment

Screening details:

Screening details:
All eligibility criteria were based on routine tests and investigations.

Period 1

Period 1 title	Phase 1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Phase 1
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab 400mg/m2 in a short iv infusion as a starting dose then a weekly dose of 250mg/m2 for 4 weeks prior to Chemoradiation (days 3, 10, 17, 24).

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral capecitabine 825 mg/m2 twice daily for 5 days in weeks 5-9

Number of subjects in period 1	Phase 1
Started	12
Completed	12

Period 2

Period 2 title	Phase 2
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Capecitabine and radiotherapy

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

Dosage and administration details:

825 mg/m2 twice daily for 5 days in weeks 1-5

Arm title	Arm B

Arm description:

Cetuximab, capecitabine and radiotherapy

Arm type	Experimental
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cetuximab 400mg/m2 in a short iv infusion as a starting dose prior to chemoradiation in weeks 1-4, and then a weekly dose of 250mg/m2 for 4 weeks after chemoradiation in weeks 10-14.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral capecitabine 825 mg/m2 twice daily weeks 5-9

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: There are 2 Baseline periods (Phase 1 and Phase 2) as two separate subsets of patients were recruited into both.

Number of subjects in period 2[2][3]	Arm A	Arm B
Started	5	5
Completed	5	4
Not completed	0	1
Consent withdrawn by subject	-	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: There are 2 Baseline periods (Phase 1 and Phase 2) as two separate subsets of patients were recruited into both.

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The Phase 1 and Phase 2 periods are not separate treatment periods but different periods in the trial. There is a separate group of patients recruited into each Phase. (i.e 12 patients in Phase 1, 10 patients in Phase 2)

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: Capecitabine and radiotherapy	
Reporting group title	Arm B
Reporting group description: Cetuximab, capecitabine and radiotherapy	

Reporting group values	Arm A	Arm B	Total
Number of subjects	5	5	10
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	61.69	63.04	
full range (min-max)	57.34 to 78.22	53.97 to 69.33	-
Gender categorical Units: Subjects			
Female	2	2	4
Male	3	3	6
Nodal status Units: Subjects			
N0	0	1	1
N1	4	2	6
N2	1	2	3
NX	0	0	0
WHO performance status Units: Subjects			
WHO 0	3	4	7
WHO 1	2	0	2
Not Reported	0	1	1
Site of tumour Units: Subjects			
Anterior	1	1	2
Posterior	0	2	2
Not known	4	2	6

Site Units: Subjects			
Lower (0 - 4.9cm)	2	2	4
Middle (5 - 9.9cm)	3	2	5
Upper (10 - 15cm)	0	1	1
Tumour stage Units: Subjects			
Tumour beyond mesorectal fascia	1	0	1
Tumour ≤ 2mm from mesorectal fascia	1	1	2
T3/T4 tumour ≤ 5cm from the anal verge	3	4	7
Glomerular filtration rate (GFR) (EDTA) Units: ml/min			
median	75	84	
full range (min-max)	54 to 143	67 to 90	-
Absolute Neutrophil Count (ANC) Units: x109/L			
median	6.4	5.7	
full range (min-max)	3.5 to 11.3	2.3 to 8.2	-
Platelets Units: x109/L			
median	286	277	
full range (min-max)	247 to 535	253 to 383	-
Bilirubin Units: µmol/L			
median	10	6	
full range (min-max)	6 to 17	4 to 9	-
Alk. Phosphatase Units: IU/L			
median	77	72	
full range (min-max)	44 to 108	66 to 94	-
Alanine Transaminase (ALT) Units: IU/L			
median	22	19	
full range (min-max)	20 to 29	8 to 22	-
CEA Units: µg/l			
median			
full range (min-max)			-
White Blood Cells Units: x109/l			
median			
full range (min-max)			-
Haemoglobin Units: g/dl			
median			
full range (min-max)			-
Magnesium Units: mmol/l			
median			
full range (min-max)			-

Subject analysis sets	
Subject analysis set title	Phase 1
Subject analysis set type	Safety analysis

Subject analysis set description:

Analysis for Phase 1 section of the trial carried out separately to Phase 2.

Reporting group values	Phase 1		
Number of subjects	12		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	65		
full range (min-max)	29 to 76		
Gender categorical Units: Subjects			
Female	1		
Male	11		
Nodal status Units: Subjects			
N0	2		
N1	4		
N2	4		
NX	2		
WHO performance status Units: Subjects			
WHO 0	7		
WHO 1	5		
Not Reported	0		
Site of tumour Units: Subjects			
Anterior Posterior Not known			
Site Units: Subjects			

Lower (0 - 4.9cm)	4		
Middle (5 - 9.9cm)	7		
Upper (10 - 15cm)	1		
Tumour stage Units: Subjects			
Tumour beyond mesorectal fascia	3		
Tumour ≤ 2mm from mesorectal fascia	5		
T3/T4 tumour ≤ 5cm from the anal verge	7		
Glomerular filtration rate (GFR) (EDTA) Units: ml/min			
median	89.3		
full range (min-max)	51.08 to 132		
Absolute Neutrophil Count (ANC) Units: x109/L			
median	4.96		
full range (min-max)	3.29 to 6.21		
Platelets Units: x109/L			
median	306		
full range (min-max)	221 to 420		
Bilirubin Units: µmol/L			
median			
full range (min-max)			
Alk. Phosphatase Units: IU/L			
median			
full range (min-max)			
Alanine Transaminase (ALT) Units: IU/L			
median			
full range (min-max)			
CEA Units: µg/l			
median	3		
full range (min-max)	1 to 45		
White Blood Cells Units: x109/l			
median	7.68		
full range (min-max)	5.88 to 9.48		
Haemoglobin Units: g/dl			
median	13.45		
full range (min-max)	9.9 to 133		
Magnesium Units: mmol/l			
median	0.88		
full range (min-max)	0.82 to 0.92		

End points

End points reporting groups

Reporting group title	Phase 1
Reporting group description: -	
Reporting group title	Arm A
Reporting group description: Capecitabine and radiotherapy	
Reporting group title	Arm B
Reporting group description: Cetuximab, capecitabine and radiotherapy	
Subject analysis set title	Phase 1
Subject analysis set type	Safety analysis
Subject analysis set description: Analysis for Phase 1 section of the trial carried out separately to Phase 2.	

Primary: Acute Toxicity (Grade 3 or above in defined DLT)

End point title	Acute Toxicity (Grade 3 or above in defined DLT)[1]
End point description:	
End point type	Primary
End point timeframe: Phase 1 and Phase 2	

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 statistics provided are descriptive only. No mathematical statistical analysis was carried out.

End point values	Arm A	Arm B	Phase 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	12	
Units: Worst adverse event experienced				
Pain Grade 3	0	0	1	
Pulmonary embolism Grade 3	0	0	1	
Rash acneiform Grade 3	0	0	2	
Diarrhea Grade 3	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Compliance with the planned dose of radiotherapy

End point title	Compliance with the planned dose of radiotherapy[2]
End point description:	
End point type	Primary

End point timeframe:

Phase 1 and Phase 2 Treatment

Notes:

[2] - 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 statistics provided are descriptive only. No mathematical statistical analysis was carried out.

End point values	Arm A	Arm B	Phase 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	4	12	
Units: Patients				
Irradiation temporarily interrupted (Yes)	3	1	1	
Irradiation temporarily interrupted (No)	2	3	11	
Reasons for interruption - (Bank Holiday)	1	1	1	
Reasons for interruption - (Intercurrent Illness)	1	0	0	
Reasons for interruption - (Toxicity)	1	0	0	
Irradiation stopped early (No)	5	4	12	
Irradiation stopped early (Yes)	0	0	0	
Total dose given at ICRU reference (45)	5	4	12	
Number of Fractions (25)	5	4	12	

Statistical analyses

No statistical analyses for this end point

Primary: Compliance with the planned dose of chemotherapy - Capecitabine compliance

End point title	Compliance with the planned dose of chemotherapy - Capecitabine compliance[3]

End point description:

End point type	Primary

End point timeframe:

Phase 1 and Phase 2 treatment

Notes:

[3] - 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 statistics provided are descriptive only. No mathematical statistical analysis was carried out.

End point values	Arm A	Arm B	Phase 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	4	12	
Units: Patients				
Reductions of capecitabine	1	0	0	
Capecitabine Adminitration Delays	3	0	1	
Any missed tablets	6	1	2	
Capecitabine stopped permanently	0	0	1	

Statistical analyses

No statistical analyses for this end point

Primary: Histopathological complete response rate

End point title	Histopathological complete response rate[4]

End point description:

End point type	Primary

End point timeframe:

Phase 1 and Phase 2

Notes:

[4] - 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 statistics provided are descriptive only. No mathematical statistical analysis was carried out.

End point values	Arm A	Arm B	Phase 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	12	
Units: Patients				
Complete response	1	1	0	
Partial response	3	2	10	
Stable disease	1	1	2	
Not done	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Compliance with the planned dose of chemotherapy - Cetuximab Compliance

End point title	Compliance with the planned dose of chemotherapy - Cetuximab Compliance[5][6]

End point description:

End point type	Primary

End point timeframe:

Phase 1 and Phase 2 treatment

Notes:

[5] - 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 statistics provided are descriptive only. No mathematical statistical analysis was carried out.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Compliance to cetuximab is only applicable to one arm as the other arm were not given cetuximab.

End point values	Arm B	Phase 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	12		
Units: Patients				
Reductions	0	0		
Delays	1	2		
Stopping permanently	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Histopathological downstaging (yPT0,T1,T2 N0) - Phase 2

End point title	Histopathological downstaging (yPT0,T1,T2 N0) - Phase 2

End point description:

End point type	Secondary

End point timeframe:

Phase 2 Surgery

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	3		
Units: Patients				
T restaging - T2 -> T0	1	0		
T restaging - T3 -> T0	0	1		
T restaging - T2 -> T1	0	1		
T restaging - T3 -> T2	1	0		
T restaging - T3 -> T3	2	1		
Regression - No tumour present	1	2		
Regression - Few tumour cells	1	1		
Regression - Moderate	1	0		
Regression - Mild	1	0		
N restaging - N0 -> N2	0	1		
N restaging - N1 -> N0	3	2		
N restaging - N1 -> N2	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Histologically confirmed (R0) resection

End point title	Histologically confirmed (R0) resection

End point description:

End point type	Secondary

End point timeframe:

Phase 1 and Phase 2 Surgery

End point values	Arm A	Arm B	Phase 1	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	3	12	
Units: Patients				
R0	4	1	8	
R1	0	2	1	
R2	0	0	1	
Not Reported	0	0	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical complications at 1 month

End point title	Surgical complications at 1 month

End point description:

End point type	Secondary

End point timeframe:

Phase 2

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	3		
Units: Event				
Anal pain Grade 1	0	1		
Hypotension Grade 1	0	1		
Vomiting Grade 1	1	0		
Rectal Pain Grade 1	1	0		
Rectal pain Grade 2	0	1		
Constipation Grade 1	1	0		
Diarrhea Grade 2	1	0		

Fatigue Grade 1	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Histopathological downstaging (yPT0,T1,T2 N0) - Phase 1

End point title	Histopathological downstaging (yPT0,T1,T2 N0) - Phase 1

End point description:

End point type	Secondary

End point timeframe:

Phase 1 Surgery

End point values	Phase 1			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Patients				
Few tumour cells	3			
Mild	4			
Moderate	2			
No tumour present	1			
Unknown	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Phase 1 and Phase 2	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0
Reporting groups	
Reporting group title	Phase 2 - Arm A
Reporting group description: Capecitabine and radiotherapy	
Reporting group title	Phase 2 - Arm B
Reporting group description: Cetuximab, capecitabine and radiotherapy	
Reporting group title	Phase 1
Reporting group description: -	

Serious adverse events	Phase 2 - Arm A	Phase 2 - Arm B	Phase 1
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	4 / 12 (33.33%)
number of deaths (all causes)	1	0	4
number of deaths resulting from adverse events			
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Allergic reaction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Phase 2 - Arm A	Phase 2 - Arm B	Phase 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	12 / 12 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 5 (100.00%)	4 / 5 (80.00%)	12 / 12 (100.00%)
occurrences (all)	5	4	12
Non-cardiac chest pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	8 / 12 (66.67%)
occurrences (all)	1	1	8
Fever			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Other: Hand/foot problem (not specified)			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	8 / 12 (66.67%)
occurrences (all)	0	0	8
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	3 / 12 (25.00%)
occurrences (all)	0	1	3
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sore throat			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Hiccups			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Other: Pulmonary embolism			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0

Confusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
GGT increased			
subjects affected / exposed	3 / 5 (60.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Neutrophil count decreased			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Other Investigations			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
White blood cell decreased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Injury, poisoning and procedural complications			
Dermatitis radiation			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Other: Moist desquamation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
Dysgeusia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0

Headache			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Paresthesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	2 / 12 (16.67%)
occurrences (all)	2	1	2
Ear and labyrinth disorders			
Other Ear and labyrinth disorders			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Blurred vision			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Other eye disorders			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 5 (80.00%)	5 / 5 (100.00%)	10 / 12 (83.33%)
occurrences (all)	4	5	10
Anal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Anal pain			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0

Constipation			
subjects affected / exposed	2 / 5 (40.00%)	3 / 5 (60.00%)	2 / 12 (16.67%)
occurrences (all)	2	3	2
Mucositis oral			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Nausia			
subjects affected / exposed	2 / 5 (40.00%)	3 / 5 (60.00%)	6 / 12 (50.00%)
occurrences (all)	2	3	6
Oral Pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Proctitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rectal pain			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	2
Abdominal Pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Dry mouth			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Dyspepsia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Other: Oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Other: PR mucinous			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Other: Rectal discharge			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Other: stomatitis/mucositis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	6 / 12 (50.00%)
occurrences (all)	0	0	6
Rectal hemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Pain of skin			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Rash acneiform			
subjects affected / exposed	0 / 5 (0.00%)	4 / 5 (80.00%)	12 / 12 (100.00%)
occurrences (all)	0	4	12
Scalp Pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Other: Brittle Nails			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Erythema multiforme			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Other: Cracked thumbs			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Other: Nail changes			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Other: Pruritis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	5 / 12 (41.67%)
occurrences (all)	0	0	5
Other: Skin disorder not specified			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Other Renal and urinary disorders			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Other: Dysuria			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Other: Lower back weakness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Nail infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Paronychia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Other Infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	1 / 12 (8.33%)
occurrences (all)	2	2	1
Hypermagnesemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hypoalbuminemia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 5 (20.00%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Hypomagnesemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2005	Update to protocol to v1.1. Amednemnts to sections 1.1 Flowchart, 3.3 End points, 6.2 Pre-treatment, 6.3 cetuximab, 6.6 Treatment modifications, 8.1 Assessments and procedures during treatment, 11.3 Sponsorship & indemnity, 14.3 Schedule of tissue collection, Appendix 3 preparation & handling of cetuximab, Appendix 5 Treatment modifications for toxicity, Appendix 8 summary of investigations
02 May 2008	Update to protocol v2.0. Updated contact details, Updated version numbers and dates, updated list of expected toxicities & updated Pharmacovigilance section
05 November 2009	Update to the protocol to v3.0 and update to Patient Information Sheet and Consent form. Updates to protocol - Minor corrections and changes to improve clarity, change in statistician, change in laboratory storing samples & NCI-CTCAE changed from v3.0 to v4.0, Tumour response assessed at 3-5 wks changed to 5-9 weeks to concur with section 8.2, Radiotherapy regimen for Arm A added as this was mistakenly omitted in previous amendment, Pharmacovigilance section amended to comply with updated regulations, Frequency of CRF completion during treatment reduced, Clarification and addition to the statistics section, Additional serum samples – weekly during chemoradiation & Use of RNAlater rather than liquid nitrogen for fresh tissue biopsies, Updated with relevant AEs from NCI-CTCAE v4.0
04 May 2010	Minor update to consent form to change the version and date of the patient information sheet that the patient has confirms they have read.
07 December 2010	Update to the patient diary cards to v2.0 to reflect the changes made when Protocol v3.0 was updated in Amendment 3
07 December 2010	Duplicated submission of Amendment 5 in error
08 April 2011	Change of Principle Investigator at Velindre Cancer Centre
21 August 2012	Updates to CTA: Change of Sponsor contact details (title, address, telephone and email), amending errors to cetuximab's brand/generic name, amending the Manufacturing Authorisation number, amendment to information concerning the modification of IMP at site.
17 December 2012	Update to protocol v4.0. Update of trial management staff, Additional section added to include information on Data Management Guidelines, Amended information within Pharmacovigilance section to reflect the most up to date protocol template, additional section added to include information on Incident reporting and Serious breaches, Additional section added to include information on Trial Monitoring and Oversight, Additional section added to reflect current protocol template, and to amend end of trial definition, Expected Adverse Events updated, Protocol history moved from page 1.
02 July 2014	site closure notification of Leeds, Beatson, Velindre & Aberdeen.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported