Clinical trial results:
A two-arm randomised trial of intermittent chemotherapy plus continuous cetuximab and of intermittent chemotherapy plus intermittent cetuximab in first line treatment of patients with K-ras Normal (wild-type) metastatic colorectal cancer

Summary

EudraCT number	2006-003049-17
Trial protocol	GB
Global end of trial date	18 January 2016

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016
Summary attachment (see zip file)	Trial Publication (COIN-B Final publication Lancet Oncology - published online 3.4.2014.pdf) Summary of results (Overview of COIN-B results for EUDRACT.pdf)

Trial information

Trial identification

Sponsor protocol code	CR11

Additional study identifiers

ISRCTN number	ISRCTN38375681
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Research Council
Sponsor organisation address	c/o Aviation house, 125 Kingsway , London, United Kingdom, WC2b 6NH
Public contact	Dr Angela Meade, Medical Research Council Clinical Trials Unit at UCL, 44 206704761, a.meade@ucl.ac.uk
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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	03 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 April 2014
Global end of trial reached?	Yes
Global end of trial date	18 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the COIN-B trial is to determine whether adding cetuximab to intermittent OxFp chemotherapy in tumours with K-raswt status, is active, safe and feasible, with the primary outcome measure of failure-free survival at 10 months.

Protection of trial subjects:

The invitation to participate in the trial will be initiated by the treating clinician who will explain the rationale for the treatment and research, and the alternative (non−trial) standard treatment options available. The patient will then be given the trial Patient Information Sheet and given a period of at least 24 hours (usually one week) to consider their decision. During this period, a telephone contact is provided so that the patient may discuss and clarify any issues with the Research Nurse or clinician. The patient information sheets will be kept by the participant for reference.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 July 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 168
Country: Number of subjects enrolled	Cyprus: 1
Worldwide total number of subjects	169
EEA total number of subjects	169

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)	88
From 65 to 84 years	81
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

July 2007 - COIN-B opened recruitment in 8 centres.
7th May 2008 - With 119 patients randomised, trial suspended due to KRAS data from global phase III randomised studies
January 2009 - reopened to recruitment following a protocol amendment to introduce KRAS screening
1st June 2010 closed to recruitment with 169 KRAS WT patients randomised

Pre-assignment

Screening details:

Following protocol amendment in November 2008, pre randomisation screening for KRAS was introduced in protocol version 3

Pre-assignment period milestones

Number of subjects started	401[1]
Intermediate milestone: Number of subjects	KRAS wild type patients: 201
Number of subjects completed	169

Pre-assignment subject non-completion reasons

Reason: Number of subjects	have KRAS Mutation: 200
Reason: Number of subjects	patient choice: 9
Reason: Number of subjects	no longer eligible: 23

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Following the trial reopening in Jan 2009 with a protocol amendment to introduce KRAS screening, a pre-assignment period was brought into being. For consistency, the "overall number enrolled" is given here as the total number randomised, since the screened patients were not enrolled as such.

Period 1

Period 1 title	Initial 12 weeks chemo + cetux
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm D

Arm description:

Intermittent chemotherapy + intermittent cetuximab

Arm type	Intermittent
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:

Please refer to protocol

Arm title	Arm E

Arm description:	
Intermittent chemotherapy + cetuximab maintenance	
Arm type	Intermittent
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:	
Please refer to protocol	

Number of subjects in period 1	Arm D	Arm E
Started	78	91
Completed	64	66
Not completed	14	25
Left trial in first 12 weeks	9	7
Death in first 12 weeks	4	14
Progression in first 12 weeks	1	4

Period 2	
Period 2 title	Trial period following initial 12 weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Arm D
Arm description:	
Intermittent chemotherapy + intermittent cetuximab	
Arm type	Intermittent
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:	
Please refer to COIN-B Protocol	
Arm title	Arm E
Arm description:	
Intermittent chemotherapy + cetuximab maintenance	
Arm type	Intermittent

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:

Please refer to protocol

Number of subjects in period 2	Arm D	Arm E
Started	64	66
Completed	48	44
Not completed	16	22
Physician decision	4	3
Treatment delay	-	1
Adverse event, non-fatal	2	5
New evidence of multiple new lesions	-	1
Intercurrent illness	1	1
patient choice	-	5
"Deranged LFT results"	1	-
Neuropathy	-	1
Urgent gynaecological referral	-	1
Lost to follow-up	5	1
Surgical resection	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Arm D
Reporting group description: Intermittent chemotherapy + intermittent cetuximab	
Reporting group title	Arm E
Reporting group description: Intermittent chemotherapy + cetuximab maintenance	

Reporting group values	Arm D	Arm E	Total
Number of subjects	78	91	169
Age categorical Units: Subjects			
<45 years	5	6	11
45-54 years	11	17	28
55-64 years	26	23	49
65-74 years	31	33	64
75+ years	5	12	17
Gender categorical Units: Subjects			
Female	30	36	66
Male	48	55	103
WHO Performance Status Units: Subjects			
Normal activity without restriction	38	40	78
Strenuous activity restricted; can do light work	35	42	77
Up and about >50% of waking hours, limited self-ca	5	9	14
Site of primary tumour Units: Subjects			
Right colon	19	22	41
Left colon	12	27	39
Rectum	25	17	42
Rectosigmoid junction	18	18	36
Transverse	4	7	11
Current status of primary tumour Units: Subjects			
Resected	41	48	89
Unresected/unresectable	34	41	75
Local recurrence	3	2	5
Timing of metastases Units: Subjects			
Metachronous	23	20	43
Synchronous	54	70	124
Missing data	1	1	2
Distribution of metastases Units: Subjects			

Liver only	16	17	33
Liver + others	39	43	82
Non-liver	22	30	52
Missing data	1	1	2
Number of metastatic sites Units: Subjects			
No sites	1	1	2
One site	28	31	59
Two sites	22	35	57
Three or more sites	27	24	51
Glomerular filtration rate Units: Subjects			
≤80ml/min	32	38	70
>80ml/min	46	53	99
Alkaline phosphatase Units: Subjects			
≥300 U/l	9	11	20
<300 U/l	69	80	149
White blood cell count Units: Subjects			
≥10,000/l	17	24	41
<10,000/l	61	67	128
Platelet count Units: Subjects			
≥400,000/l	17	20	37
<400,000/l	61	71	132

End points

End points reporting groups

Reporting group title	Arm D
Reporting group description:	
Intermittent chemotherapy + intermittent cetuximab	
Reporting group title	Arm E
Reporting group description:	
Intermittent chemotherapy + cetuximab maintenance	
Reporting group title	Arm D
Reporting group description:	
Intermittent chemotherapy + intermittent cetuximab	
Reporting group title	Arm E
Reporting group description:	
Intermittent chemotherapy + cetuximab maintenance	

Primary: 10-month failure-free survival rate

End point title	10-month failure-free survival rate
End point description:	

End point type	Primary
End point timeframe:	
The point at which at least half of the randomised patients on the intermittent cetuximab arm (Arm D) with KRAS wild-type tumours can be declared failure-free 10 months after randomisation	

End point values	Arm D	Arm E		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: Failure-free at 10 months				
Failure free at 10 months	32	34		
Failed at or before 10 months	27	20		
Failure status unknown at or before 10 months	5	12		

Statistical analyses

Statistical analysis title	10-month failure-free survival rate (Arm D)
Statistical analysis description:	
The proportion of randomised patients, with KRAS wild-type tumours and who completed their initial 12 weeks of combination chemo + cetuximab, who did not experience death or disease progression within 10 months of randomisation. N.B. Arm E is *not* involved in this analysis, but the database will not accept single arm analyses within a trial defined as having two arms! Hence, the true number of subjects in this analysis is 64.	
Comparison groups	Arm D v Arm E

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Percentage
Point estimate	50
Confidence interval	
level	95 %
sides	1-sided
lower limit	39

Notes:

[1] - An exact binomial test that the observed 10-month failure-free survival rate has a one-sided 95% confidence limit that excludes 35%.

Statistical analysis title	10-month failure-free survival rate (Arm E)

Statistical analysis description:

The proportion of randomised patients, with KRAS wild-type tumours and who completed their initial 12 weeks of combination chemo + cetuximab, who did not experience death or disease progression within 10 months of randomisation.

N.B. Arm D is *not* involved in this analysis, but the database will not accept single arm analyses within a trial defined as having two arms! Hence, the true number of subjects in this analysis is 66.

Comparison groups	Arm E v Arm D
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Percentage
Point estimate	52
Confidence interval	
level	95 %
sides	1-sided
lower limit	41

Notes:

[2] - An exact binomial test that the observed 10-month failure-free survival rate has a one-sided 95% confidence limit that excludes 35%.

Secondary: Failure-free survival (PPA)

End point title	Failure-free survival (PPA)

End point description:

Median + IQR failure-free survival by arm, among patients with KRAS wild-type tumours who successfully completed their initial 12 weeks of combination chemo + cetuximab. Patients without an event were censored either at the limit of their observed follow-up or at the analysis date of 24th April 2012.

End point type	Secondary

End point timeframe:

Time from randomisation among patients with KRAS wild-type tumours who successfully completed their initial 12 weeks of combination chemo + cetuximab.

End point values	Arm D	Arm E		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: Months				
median (inter-quartile range (Q1-Q3))	12.2 (6 to 23.4)	14.3 (8.7 to 23.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Failure-free survival (ITT)

End point title	Failure-free survival (ITT)

End point description:

Median + IQR failure-free survival by arm, among all randomised patients with KRAS wild-type tumours. Patients without an event were censored either at the limit of their observed follow-up or at the analysis date of 24th April 2012.

End point type	Secondary

End point timeframe:

Time from randomisation among all randomised patients with KRAS wild-type tumours.

End point values	Arm D	Arm E		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	91		
Units: Months				
median (inter-quartile range (Q1-Q3))	12.1 (5 to 23.4)	12 (6.1 to 22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (ITT)

End point title	Overall survival (ITT)

End point description:

Median + IQR overall survival by arm, among all randomised patients with KRAS wild-type tumours. Patients without an event were censored either at the limit of their observed follow-up or at the analysis date of 24th April 2012.

End point type	Secondary

End point timeframe:

Time from randomisation among all randomised patients with KRAS wild-type tumours.

End point values	Arm D	Arm E		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	91		
Units: Months				
median (inter-quartile range (Q1-Q3))	16 (8.9 to 30.9)	17.5 (6.4 to 29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival in the interval

End point title	Progression-free survival in the interval

End point description:

Survival (time-to-event) analysis.
For Arm D patients, this is equivalent to time to first progression within the intermittent phase of their treatment.

End point type	Secondary

End point timeframe:

Time from end of initial 12 weeks of continuous chemo + cetuximab to first progression or death.

End point values	Arm D	Arm E		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	66		
Units: Months				
median (inter-quartile range (Q1-Q3))	3.1 (2.1 to 8.1)	5.8 (2.9 to 11.2)		

Statistical analyses

Statistical analysis title	Cox regression analysis

Statistical analysis description:

A Cox regression analysis comparing survival between the two arms in the intermittent phase of treatment (i.e. after the initial 12 weeks of continuous treatment in both arms).

Comparison groups	Arm E v Arm D
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.01

Secondary: 12-week response

End point title	12-week response

End point description:

Disease response after 12 weeks of treatment, as measured by RECIST.

End point type	Secondary

End point timeframe:

12 weeks after randomisation (in practice, measurements between 8 and 16 weeks were included)

End point values	Arm D	Arm E		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	91		
Units: Patients				
Complete response	1	1		
Partial response	48	38		
Stable disease	8	14		
Progressive disease	7	7		
Assessment done but result missing	1	0		
No assessment done	13	31		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified indefinitely after randomisation.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTC
Dictionary version	3.0

Reporting groups

Reporting group title	Arm D

Reporting group description:

Intermittent chemotherapy + intermittent cetuximab

Reporting group title	Arm E

Reporting group description:

Intermittent chemotherapy + cetuximab maintenance

Serious adverse events	Arm D	Arm E	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 112 (56.25%)	63 / 114 (55.26%)	
number of deaths (all causes)	99	107	
number of deaths resulting from adverse events			
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 112 (3.57%)	3 / 114 (2.63%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombosis in device	Additional description: Reported as "Thrombosis- venous access device"		
subjects affected / exposed	0 / 112 (0.00%)	5 / 114 (4.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
SVC obstruction	Additional description: Reported as "Vascular- other (SVC obstruction)"		

subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visceral arterial ischaemia	Additional description: Reported as "Visceral arterial ischaemia- bowel"		
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 112 (2.68%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Reported as "fever"		
subjects affected / exposed	2 / 112 (1.79%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 112 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pain - abdominal			
subjects affected / exposed	3 / 112 (2.68%)	5 / 114 (4.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain - other	Additional description: Back; kidney; headache		
subjects affected / exposed	3 / 112 (2.68%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	5 / 112 (4.46%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	3 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 112 (1.79%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular tachyarrhythmia	Additional description: Described as "Supraventricular arrhythmia" and as "Supraventricular arrhythmia- atrial fibrilation"		
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope	Additional description: Reported as "Vasovagal episode"		
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infarction	Additional description: Reported as "Cardiac ischaemia/ infarction"		

subjects affected / exposed	1 / 112 (0.89%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS Cerebrovascular Ischaemia			
subjects affected / exposed	3 / 112 (2.68%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Brain metastases			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation	Additional description: Reported as "Confusion"		
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillen Barre-like syndrome			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction	Additional description: Reported as "neuropathy: motor"		

subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina compression			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	3 / 112 (2.68%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	2 / 112 (1.79%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	11 / 112 (9.82%)	8 / 114 (7.02%)	
occurrences causally related to treatment / all	5 / 13	6 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis management			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 112 (1.79%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction			
subjects affected / exposed	7 / 112 (6.25%)	4 / 114 (3.51%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Perforation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	3 / 112 (2.68%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection related reaction	Additional description: Reported as "Injection site reaction/ extravasation changes"		
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 112 (0.00%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Ureteric obstruction			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 112 (0.89%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic floor muscle weakness			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia	Additional description: Includes "neutropenic sepsis"		
subjects affected / exposed	14 / 112 (12.50%)	10 / 114 (8.77%)	
occurrences causally related to treatment / all	2 / 15	4 / 11	
deaths causally related to treatment / all	0 / 0	1 / 2	

Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Magnesium deficiency	Additional description: Reported as "Magnesium, serum- low"		
subjects affected / exposed	2 / 112 (1.79%)	3 / 114 (2.63%)	
occurrences causally related to treatment / all	2 / 3	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bilirubinuria	Additional description: Reported as "metabolic/laboratory- bilirubin, AST, ALP"		
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm D	Arm E	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 112 (99.11%)	109 / 114 (95.61%)	
Nervous system disorders			
Peripheral neuropathy	Additional description: G2+ CTC toxicity		
subjects affected / exposed	36 / 112 (32.14%)	28 / 114 (24.56%)	
occurrences (all)	76	74	
General disorders and administration site conditions			
Pain	Additional description: G2+ CTC toxicity		
subjects affected / exposed	50 / 112 (44.64%)	60 / 114 (52.63%)	
occurrences (all)	110	131	
Lethargy	Additional description: G2+ CTC toxicity		
subjects affected / exposed	72 / 112 (64.29%)	69 / 114 (60.53%)	
occurrences (all)	240	212	
Vein pain	Additional description: G2+ CTC toxicity		
subjects affected / exposed	3 / 112 (2.68%)	4 / 114 (3.51%)	
occurrences (all)	3	5	
Blood and lymphatic system disorders			

Platelet count	Additional description: G2+ CTC toxicity		
subjects affected / exposed	12 / 112 (10.71%)	18 / 114 (15.79%)	
occurrences (all)	28	21	
Haemoglobin	Additional description: G2+ CTC toxicity		
subjects affected / exposed	49 / 112 (43.75%)	39 / 114 (34.21%)	
occurrences (all)	98	77	
White blood cell count	Additional description: G2+ CTC toxicity		
subjects affected / exposed	39 / 112 (34.82%)	36 / 114 (31.58%)	
occurrences (all)	96	57	
Neutrophil count	Additional description: G2+ CTC toxicity		
subjects affected / exposed	53 / 112 (47.32%)	50 / 114 (43.86%)	
occurrences (all)	127	75	
Hypermagnesaemia	Additional description: G2+ CTC toxicity		
subjects affected / exposed	15 / 112 (13.39%)	19 / 114 (16.67%)	
occurrences (all)	22	50	
Gastrointestinal disorders			
Nausea	Additional description: CTC G2+ toxicity		
subjects affected / exposed	33 / 112 (29.46%)	30 / 114 (26.32%)	
occurrences (all)	57	47	
Vomiting	Additional description: CTC G2+ toxicity		
subjects affected / exposed	30 / 112 (26.79%)	24 / 114 (21.05%)	
occurrences (all)	43	32	
Anorexia	Additional description: G2+ CTC toxicity		
subjects affected / exposed	48 / 112 (42.86%)	37 / 114 (32.46%)	
occurrences (all)	90	64	
Diarrhoea	Additional description: G2+ CTC toxicity		
subjects affected / exposed	51 / 112 (45.54%)	50 / 114 (43.86%)	
occurrences (all)	123	92	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: G2+ CTC toxicity		
subjects affected / exposed	1 / 112 (0.89%)	5 / 114 (4.39%)	
occurrences (all)	2	7	
Nail disorder	Additional description: G2+ CTC toxicity "Nail changes"		
subjects affected / exposed	19 / 112 (16.96%)	24 / 114 (21.05%)	
occurrences (all)	29	55	
Rash	Additional description: G2+ CTC toxicity		

subjects affected / exposed	77 / 112 (68.75%)	72 / 114 (63.16%)	
occurrences (all)	236	253	
Hand-foot syndrome	Additional description: G2+ CTC toxicity		
subjects affected / exposed	38 / 112 (33.93%)	50 / 114 (43.86%)	
occurrences (all)	88	122	
Infections and infestations			
Stomatitis	Additional description: G2+ CTC toxicity		
subjects affected / exposed	56 / 112 (50.00%)	53 / 114 (46.49%)	
occurrences (all)	135	129	
Product issues			
Hypersensitivity	Additional description: G2+ CTC toxicity "Cetuximab hypersensitivity"		
subjects affected / exposed	6 / 112 (5.36%)	6 / 114 (5.26%)	
occurrences (all)	10	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2007	To become version 2.0 of protocol - Evidence from the main COIN trial that the combination of XELOX plus cetuximab is causing unacceptably high level of GI toxicity. - The introduction of a parallel sub-study to run alongside COIN and COIN-B for any centres who wish to take part. Further information about the sub-study is included in a new Appendix to the main protocol.
17 November 2008	To become version 3.0 of protocol: Re-opening of the trial following suspension and the introduction of KRAS screening prior to randomisation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 May 2008	Trial suspended due to KRAS data from global phase III randomised studies.	05 January 2009

Notes:

Limitations and caveats

None reported