Clinical trial results:
A randomised open-labelled multicentre trial of the efficacy of epirubicin, oxaliplatin and capecitabine (EOX) with or without panitumumab in previously untreated advanced oesophago-gastric cancer (REAL3)

Summary

EudraCT number	2007-005976-15
Trial protocol	GB
Global end of trial date	28 February 2014

Results information

Result version number	v1 (current)
This version publication date	14 June 2019
First version publication date	14 June 2019

Trial information

Trial identification

Sponsor protocol code	CCR3024

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Royal Marsden NHS Foundation Trust
Sponsor organisation address	Downs Road, Sutton, London, United Kingdom, sm25pt
Public contact	Claire Saffery, The Royal Marsden NHS Foundation Trust, 020 8661 3637, claire.saffery@rmh.nhs.uk
Scientific contact	Claire Saffery, The Royal Marsden NHS Foundation Trust, 020 8661 3637, claire.saffery@rmh.nhs.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	16 July 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 July 2012
Global end of trial reached?	Yes
Global end of trial date	28 February 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether adding panitumumab to standard chemotherapy with epirubicin, oxaliplatin and capecitabine (EOX), improves the median overall survival of patients with advanced oesophago-gastric cancer.

Protection of trial subjects:

Any safety concerns generated from this or other studies of panitumumab could lead to stopping this trial
prematurely. Serious adverse events will be reported and evaluated regularly. Any significant observations would
result in a formal review and dependent upon the outcome of that review, the study would be terminated or continue.
Serious adverse events are also reported to the regulatory authorities within timelines dicated by law.
Interim analyses will take place approximately annually to examine safety, scientific validity and the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 June 2008
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	United Kingdom: 553
Worldwide total number of subjects	553
EEA total number of subjects	553

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)	326
From 65 to 84 years	227
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The following assessments will take place during the screening period; Clinical examination & history, WHO performance status, CT scan (chest/abdomen/pelvis), Full blood count, Serum biochemistry, Creatinine clearance, ECG, Pregnancy testing, Quality of life, Biomarkers

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	EOC alone

Arm description:

epirubicin, oxaliplatin and capecitabine.

Arm type	Active comparator
Investigational medicinal product name	epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

50mg/m2 IV on day 1.

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

130mg/m2 IV on day 1.

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

Dosage and administration details:

1250mg/m2 PO in two divided doses continuously from days 1-21.

Arm title	EOC + Panitumumab

Arm description:

epirubicin, oxaliplatin, capecitabine and panitumumab

Arm type	Active comparator

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 50mg/m2 IV on day 1.	
Investigational medicinal product name	oxaliplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 100mg/m2 IV on day 1.	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1000mg/m2 PO in two divided doses continuously from days 1-21.	
Investigational medicinal product name	Panitumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intrauterine use
Dosage and administration details: 9mg/kg IV on day 1 of each cycle after mEOX chemotherapy.	

Number of subjects in period 1	EOC alone	EOC + Panitumumab
Started	275	278
Completed	266	276
Not completed	9	2
Consent withdrawn by subject	4	-
Physician decision	5	1
Had not started prior to study closure	-	1

Baseline characteristics

Reporting groups	
Reporting group title	EOC alone
Reporting group description: epirubicin, oxaliplatin and capecitabine.	
Reporting group title	EOC + Panitumumab
Reporting group description: epirubicin, oxaliplatin, capecitabine and panitumumab	

Reporting group values	EOC alone	EOC + Panitumumab	Total
Number of subjects	275	278	553
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	168	158	326
From 65-84 years	107	120	227
85 years and over	0	0	0
Age continuous Units: years			
median	62	63	
inter-quartile range (Q1-Q3)	54 to 68	56 to 68	-
Gender categorical Units: Subjects			
Female	49	46	95
Male	226	232	458

Subject analysis sets	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomised to the study analysed according to the arm to which they were initially randomised.
However, patients still on treatment on the 19th October 2011 were censored at this point to ensure that the crossover of patients to standard chemotherapy does not interfere with this analysis.

Reporting group values	Intention to treat		
Number of subjects	553		
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	 326 227 		
Age continuous Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female Male	95 458		

End points

End points reporting groups

Reporting group title	EOC alone
Reporting group description:	
epirubicin, oxaliplatin and capecitabine.	
Reporting group title	EOC + Panitumumab
Reporting group description:	
epirubicin, oxaliplatin, capecitabine and panitumumab	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomised to the study analysed according to the arm to which they were initially randomised. However, patients still on treatment on the 19th October 2011 were censored at this point to ensure that the crossover of patients to standard chemotherapy does not interfere with this analysis.	

Primary: Overall survival at 1 year

End point title	Overall survival at 1 year
End point description:	
Time from Randomisation to death or censored at time last followed up. Data for patients still on treatment were censored at the time of crossover to allow accurate comparison between 2 trial groups.	
End point type	Primary
End point timeframe:	
One year post last patient randomised	

End point values	EOC alone	EOC + Panitumumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	275	278		
Units: survival percent alive				
number (confidence interval 95%)	46 (38 to 54)	33 (26 to 41)		

Statistical analyses

Statistical analysis title	Overll Survival
Statistical analysis description:	
Overall survival was estimated the Kaplan-Meier method. Groups were compared with the log-rank test and Cox regression analysis to generate Hazard Ratios and 95% CIs.	
Comparison groups	EOC + Panitumumab v EOC alone

Number of subjects included in analysis	553
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.76

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to 30 days post last trial treatment

Adverse event reporting additional description:

Grade 3-5 toxicities

Assessment type	Systematic

Dictionary used

Dictionary name	No dictionary
Dictionary version	0

Reporting groups

Reporting group title	EOC alone

Reporting group description: -

Reporting group title	EOC + Panitumumab

Reporting group description: -

Serious adverse events	EOC alone	EOC + Panitumumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	125 / 266 (46.99%)	133 / 276 (48.19%)	
number of deaths (all causes)	110	141	
number of deaths resulting from adverse events	8	5	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 266 (0.75%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders - Other, specify			
subjects affected / exposed	0 / 266 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			

subjects affected / exposed	0 / 266 (0.00%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 266 (3.38%)	6 / 276 (2.17%)	
occurrences causally related to treatment / all	10 / 10	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	2 / 266 (0.75%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction			
subjects affected / exposed	1 / 266 (0.38%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	11 / 266 (4.14%)	9 / 276 (3.26%)	
occurrences causally related to treatment / all	9 / 13	8 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction to excipient			
subjects affected / exposed	3 / 266 (1.13%)	3 / 276 (1.09%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 266 (1.50%)	3 / 276 (1.09%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			

subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neurology - Other (Specify)			
subjects affected / exposed	3 / 266 (1.13%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hemoglobin increased			
subjects affected / exposed	9 / 266 (3.38%)	4 / 276 (1.45%)	
occurrences causally related to treatment / all	1 / 9	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine increased			
subjects affected / exposed	3 / 266 (1.13%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haptoglobin decreased			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	7 / 266 (2.63%)	8 / 276 (2.90%)	
occurrences causally related to treatment / all	7 / 7	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	3 / 266 (1.13%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Fracture			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation recall reaction (dermatologic)			
subjects affected / exposed	3 / 266 (1.13%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	12 / 266 (4.51%)	17 / 276 (6.16%)	
occurrences causally related to treatment / all	12 / 12	18 / 18	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac disorders			
Cardiac infarction			
subjects affected / exposed	4 / 266 (1.50%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	2 / 2	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 266 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemia			
subjects affected / exposed	1 / 266 (0.38%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 266 (0.38%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal reaction			
subjects affected / exposed	1 / 266 (0.38%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Peripheral sensory neuropathy			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (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			
Febrile neutropenia			
subjects affected / exposed	32 / 266 (12.03%)	19 / 276 (6.88%)	
occurrences causally related to treatment / all	36 / 36	22 / 22	
deaths causally related to treatment / all	2 / 2	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 266 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 266 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 266 (0.75%)	5 / 276 (1.81%)	
occurrences causally related to treatment / all	1 / 2	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	40 / 266 (15.04%)	51 / 276 (18.48%)	
occurrences causally related to treatment / all	50 / 50	62 / 63	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	3 / 266 (1.13%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal fistula			
subjects affected / exposed	0 / 266 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoids			
subjects affected / exposed	0 / 266 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophagitis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	14 / 266 (5.26%)	20 / 276 (7.25%)	
occurrences causally related to treatment / all	18 / 19	22 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	29 / 266 (10.90%)	29 / 276 (10.51%)	
occurrences causally related to treatment / all	31 / 36	39 / 41	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders - Other, specify			
subjects affected / exposed	0 / 266 (0.00%)	3 / 276 (1.09%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hemorrhage			
subjects affected / exposed	5 / 266 (1.88%)	6 / 276 (2.17%)	
occurrences causally related to treatment / all	1 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constitutional symptoms			
subjects affected / exposed	2 / 266 (0.75%)	4 / 276 (1.45%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perforation, GI – Select			
subjects affected / exposed	1 / 266 (0.38%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 266 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 266 (0.00%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal and urinary disorders - Other, specify			
subjects affected / exposed	2 / 266 (0.75%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorder - Other, specify			
subjects affected / exposed	1 / 266 (0.38%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	19 / 266 (7.14%)	30 / 276 (10.87%)	
occurrences causally related to treatment / all	17 / 19	43 / 49	
deaths causally related to treatment / all	0 / 0	3 / 3	
pulmonary			
subjects affected / exposed	1 / 266 (0.38%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anorexia nervosa			
subjects affected / exposed	1 / 266 (0.38%)	4 / 276 (1.45%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	18 / 266 (6.77%)	13 / 276 (4.71%)	
occurrences causally related to treatment / all	19 / 21	14 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 266 (0.00%)	1 / 276 (0.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			

subjects affected / exposed	0 / 266 (0.00%)	2 / 276 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalemia			
subjects affected / exposed	4 / 266 (1.50%)	4 / 276 (1.45%)	
occurrences causally related to treatment / all	4 / 4	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 266 (0.00%)	9 / 276 (3.26%)	
occurrences causally related to treatment / all	0 / 0	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic/Lab - Other (Specify)			
subjects affected / exposed	3 / 266 (1.13%)	0 / 276 (0.00%)	
occurrences causally related to treatment / all	2 / 3	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	EOC alone	EOC + Panitumumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	166 / 266 (62.41%)	187 / 276 (67.75%)	
Nervous system disorders			
Lethargy			
subjects affected / exposed	35 / 266 (13.16%)	48 / 276 (17.39%)	
occurrences (all)	35	48	
Peripheral motor neuropathy			
subjects affected / exposed	18 / 266 (6.77%)	4 / 276 (1.45%)	
occurrences (all)	18	4	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	37 / 266 (13.91%)	20 / 276 (7.25%)	
occurrences (all)	37	20	
Neutropenia			
subjects affected / exposed	74 / 266 (27.82%)	35 / 276 (12.68%)	
occurrences (all)	74	35	

Anaemia			
subjects affected / exposed	15 / 266 (5.64%)	11 / 276 (3.99%)	
occurrences (all)	15	11	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	23 / 266 (8.65%)	23 / 276 (8.33%)	
occurrences (all)	23	23	
Mucositis management			
subjects affected / exposed	0 / 266 (0.00%)	14 / 276 (5.07%)	
occurrences (all)	0	14	
Diarrhoea			
subjects affected / exposed	30 / 266 (11.28%)	48 / 276 (17.39%)	
occurrences (all)	30	48	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	11 / 266 (4.14%)	20 / 276 (7.25%)	
occurrences (all)	11	20	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 266 (0.75%)	29 / 276 (10.51%)	
occurrences (all)	2	29	
Hand-foot-syndrome			
subjects affected / exposed	13 / 266 (4.89%)	16 / 276 (5.80%)	
occurrences (all)	13	16	
Infections and infestations			
Infection			
subjects affected / exposed	33 / 266 (12.41%)	28 / 276 (10.14%)	
occurrences (all)	33	28	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	16 / 266 (6.02%)	10 / 276 (3.62%)	
occurrences (all)	16	10	
Hypomagnesaemia			
subjects affected / exposed	0 / 266 (0.00%)	13 / 276 (4.71%)	
occurrences (all)	0	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2008	Update on capecitabine dose for patients on ARM2 Inclusion criteria updated to reflect that patients receiving palliative radiotherapy to sites of disease that are not measurable may be eligible and should be discussed with the chief investigator. Guidance for duration of panitumumab administration for larger patients updated. Info regarding pre medication for panitumumab updated. Updated guidance for capping surface area for largewr patients. Instructions to take water with capecitiabine included. Dose banding for cape for patients in Arm B updated. Additional guidance for management of neutropenia with infection/fever, neutrophil count, renal toc, neurotox, palmar plantarerythmia and allergic reactions. Clarification that certain investigations must take place within 7 days prior to randomization. Updated guidance for management of blood specimens. Updated info stating that copies of all SARs should be copied to Amgen ltd Panitumumab accountability updated.
01 October 2008	Starting dose for panitumumab for dose level -2 updated. amendment to doses for EOX following dose level implementation. Further dose reduction for cape and oxali implemented due to a further case of G3 diarhoea and G5 infection. Updated guidance for the management of diarhoea.
01 April 2009	The word Experimental changed to investigational changes throughout. Dose level clarifications provided.
30 July 2009	Subsection regarding the safety analysis of dose finding exercise added. Information regarding trial team meetings added.
01 December 2009	EOX in Arm B is referred to as mEOX (modified EOX) throughout. Panitumumab dose is confirmed as 9mg/kg. Cape dose in arm b is confirmed as 1000mg/m2 Results of dosefinding exercise and reason for choice of dose level 0 inserted. Two fatal infusion reactions to panitumumab have been included in the protocol. Background section updated with the resilts of two phase III studies of Pan presented in 2009. Removal of details of dose finding exercise. Now situated in appendix I. Insertion of text regarding management of diarrhea. Insetion of text stating that use of aprepitant is permitted. Removal of dose banding tables for dose level 1. Clairification for procedure regarding blood samples. Addition of KRas wild type versus mutant as an exploratory sub group analysis.

12 July 2010	Update on the number of patients treated with Panitumumab included. Info on preemptice treatment o reduce likelihood of grade 2 skin tox. Addition of the use of a second quality of life form EQ-5D. ALT or AST can be done, doesn't have to be both. EGFR and KRAS wild type are not required for study entry. Saline volume requirements updated. Infustion reactions guidance updated. Skin tox management updated. Dose banding for epi and oxali using local practice is updated. Guidance for management of persistant fatigue updated. Inclusion of O'Rouke dysphagia grading.
12 January 2011	Sample size updated. Info that consent must be taken by a clinician only. Doxycycline dose updated. Additional text regarding the first 10 patients who were randomized to arm b with a different dose. Information amended regarding the formal no-comparative interim analysis. Information regarding the interim analysis updated.
31 March 2011	Information regarding the continued use of panitumumab past 8 cycles included. Panitumumab monotherapy and 12 week CT scans included. Rationale for continuing panitumumab until disease progression inserted. Information regarding the exclusion of the first 19 patients randomized during the dose finding phase. Clarity of assessments which should take place during treatment. UPdated information regarding when quality of life questionnaires should be completed. Additional text regarding follow up after disease progression. Additional text regarding an additional optional blood test and biopsy for ARM B patients. Additional text regarding the sensitivity analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported